# TABLE OF APPENDIX

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: December 23, 2022

SUBJECT: Review of Supplemental Drug Applications Proposing Modifications to the Mifepristone REMS Program

FDA is currently reviewing a supplemental new drug application from Danco Laboratories, LLC (Danco) and a supplemental abbreviated new drug application from GenBioPro, Inc. (GBP) that propose to modify the Mifepristone Risk Evaluation and Mitigation Strategy (REMS) Program as approved under Danco's new drug application for Mifeprex (mifepristone) (NDA 020867) and GBP's abbreviated new drug application for Mifepristone Tablets 200 mg (ANDA 091178). Citing the Comstock Act, 18 U.S.C. §§ 1461, 1462, Plaintiffs in *Alliance for Hippocratic Medicine v. U.S. Food and Drug Administration*, No. 2:22-cv-00223-Z (N.D. Tex.), have alleged that FDA's actions regarding mifepristone do not comply with "federal laws that expressly prohibit the mailing or delivery by any letter carrier, express company, or other common carrier of any substance or drug intended for producing abortion" and also that FDA "failed to acknowledge and address" those laws. Complaint ¶¶ 22, 392 (Nov. 18, 2022). This memorandum notes that the Office of Legal Counsel of the United States Department of Justice, which provides controlling advice to Executive Branch officials on questions of law, has concluded that the Comstock Act provisions cited by Plaintiffs "[do] not prohibit the mailing of mifepristone or misoprostol where the sender lacks the intent that the recipient will use them unlawfully. And in light of the many lawful uses of mifepristone and misoprostol, the fact that these drugs are being mailed to a jurisdiction that significantly restricts abortion is not a sufficient basis for concluding that the mailing violates [these provisions]." Memorandum for Thomas J. Marshall, General Counsel, United States Postal Service, from Christopher H. Schroeder, Assistant Attorney General, Office of Legal Counsel, *Re: Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortions*, at 15 (December 23, 2022).[1] Thus, even if the Comstock Act provisions bear on FDA's analysis of the pending supplemental drug applications, in light of the conclusions set forth by the Office of Legal Counsel, they pose no issue for FDA's approval of the applications.

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[1] The Office of Legal Counsel's analysis applies to 18 U.S.C. § 1461 and § 1462. *See id.* at 1 n.3.

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

The association for medical ultrasound
aium
AMERICAN INSTITUTE OF ULTRASOUND IN MEDICINE

Society for Maternal•Fetal Medicine
High-risk pregnancy experts

# COMMITTEE OPINION

Number 700 • May 2017 *(Replaces Committee Opinion Number 611, October 2014)*

**Committee on Obstetric Practice**
**American Institute of Ultrasound in Medicine**
**Society for Maternal–Fetal Medicine**

*This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, in collaboration with members Christian M. Pettker, MD; James D. Goldberg, MD; and Yasser Y. El-Sayed, MD; the American Institute of Ultrasound in Medicine's liaison member Joshua A. Copel, MD; and the Society for Maternal–Fetal Medicine.*

*This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.*

# Methods for Estimating the Due Date

**ABSTRACT:** Accurate dating of pregnancy is important to improve outcomes and is a research and public health imperative. As soon as data from the last menstrual period, the first accurate ultrasound examination, or both are obtained, the gestational age and the estimated due date (EDD) should be determined, discussed with the patient, and documented clearly in the medical record. Subsequent changes to the EDD should be reserved for rare circumstances, discussed with the patient, and documented clearly in the medical record. A pregnancy without an ultrasound examination that confirms or revises the EDD before 22 0/7 weeks of gestational age should be considered suboptimally dated. When determined from the methods outlined in this document for estimating the due date, gestational age at delivery represents the best obstetric estimate for the purpose of clinical care and should be recorded on the birth certificate. For the purposes of research and surveillance, the best obstetric estimate, rather than estimates based on the last menstrual period alone, should be used as the measure for gestational age.

## Recommendations

The American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal–Fetal Medicine make the following recommendations regarding the method for estimating gestational age and due date:

- Ultrasound measurement of the embryo or fetus in the first trimester (up to and including 13 6/7 weeks of gestation) is the most accurate method to establish or confirm gestational age.
- If pregnancy resulted from assisted reproductive technology (ART), the ART-derived gestational age should be used to assign the estimated due date (EDD). For instance, the EDD for a pregnancy that resulted from in vitro fertilization should be assigned using the age of the embryo and the date of transfer.
- As soon as data from the last menstrual period (LMP), the first accurate ultrasound examination, or both are obtained, the gestational age and the EDD should be determined, discussed with the patient, and documented clearly in the medical record. Subsequent changes to the EDD should be reserved for rare circumstances, discussed with the patient, and documented clearly in the medical record.
- When determined from the methods outlined in this document for estimating the due date, gestational age at delivery represents the best obstetric estimate for the purpose of clinical care and should be recorded on the birth certificate. For the purposes of research and surveillance, the best obstetric estimate, rather than estimates based on the LMP alone, should be used as the measure for gestational age.

- A pregnancy without an ultrasound examination that confirms or revises the EDD before 22 0/7 weeks of gestational age should be considered suboptimally dated.

## Introduction

An accurately assigned EDD early in prenatal care is among the most important results of evaluation and history taking. This information is vital for timing of appropriate obstetric care; scheduling and interpretation of certain antepartum tests; determining the appropriateness of fetal growth; and designing interventions to prevent preterm births, postterm births, and related morbidities. Appropriately performed obstetric ultrasonography has been shown to accurately determine fetal gestational age (1). A consistent and exacting approach to accurate dating is also a research and public health imperative because of the influence of dating on investigational protocols and vital statistics. This Committee Opinion outlines a standardized approach to estimate gestational age and the anticipated due date. It is understood that within the ranges suggested by different studies, no perfect evidence exists to establish a single-point cutoff in the difference between clinical and ultrasonographic EDD to prompt changing a pregnancy's due date. However, there is great usefulness in having a single, uniform standard within and between institutions that have access to high-quality ultrasonography (as most, if not all, U.S. obstetric facilities do). Accordingly, in creating recommendations and the associated summary table, single-point cutoffs were chosen based on expert review.

## Background

Traditionally, determining the first day of the LMP is the first step in establishing the EDD. By convention, the EDD is 280 days after the first day of the LMP. Because this practice assumes a regular menstrual cycle of 28 days, with ovulation occurring on the 14th day after the beginning of the menstrual cycle, this practice does not account for inaccurate recall of the LMP, irregularities in cycle length, or variability in the timing of ovulation. It has been reported that approximately one half of women accurately recall their LMP (2–4). In one study, 40% of the women randomized to receive first-trimester ultrasonography had their EDD adjusted because of a discrepancy of more than 5 days between ultrasound dating and LMP dating (5). Estimated due dates were adjusted in only 10% of the women in the control group who had ultrasonography in the second trimester, which suggests that first-trimester ultrasound examination can improve the accuracy of the EDD, even when the first day of the LMP is known.

Accurate determination of gestational age can positively affect pregnancy outcomes. For instance, one study found a reduction in the need for postterm inductions in a group of women randomized to receive routine first-trimester ultrasonography compared with women who received only second-trimester ultrasonography (5). A Cochrane review concluded that ultrasonography can reduce the need for postterm induction and lead to earlier detection of multiple gestations (6). Because decisions to change the EDD significantly affect pregnancy management, their implications should be discussed with patients and recorded in the medical record.

## Clinical Considerations in the First Trimester

Ultrasound measurement of the embryo or fetus in the first trimester (up to and including 13 6/7 weeks of gestation) is the most accurate method to establish or confirm gestational age (3, 4, 7–10). Up to and including 13 6/7 weeks of gestation, gestational age assessment based on measurement of the crown–rump length (CRL) has an accuracy of ±5–7 days (11–14). Measurements of the CRL are more accurate the earlier in the first trimester that ultrasonography is performed (11, 15–18). The measurement used for dating should be the mean of three discrete CRL measurements when possible and should be obtained in a true midsagittal plane, with the genital tubercle and fetal spine longitudinally in view and the maximum length from cranium to caudal rump measured as a straight line (8, 11). Mean sac diameter measurements are not recommended for estimating the due date. Beyond measurements of 84 mm (corresponding to approximately 14 0/7 weeks of gestation), the accuracy of the CRL to estimate gestational age decreases, and in these cases, other second-trimester biometric parameters (discussed in the following section) should be used for dating. If ultrasound dating before 14 0/7 weeks of gestation differs by more than 7 days from LMP dating, the EDD should be changed to correspond with the ultrasound dating. Dating changes for smaller discrepancies are appropriate based on how early in the first trimester the ultrasound examination was performed and clinical assessment of the reliability of the LMP date (Table 1). For instance, before 9 0/7 weeks of gestation, a discrepancy of more than 5 days is an appropriate reason for changing the EDD. If the patient is unsure of her LMP, dating should be based on ultrasound examination estimates (ideally obtained before or at 13 6/7 weeks of gestation), with the earliest ultrasound examination of a CRL measurement prioritized as the most reliable.

If pregnancy resulted from ART, the ART-derived gestational age should be used to assign the EDD. For instance, the EDD for a pregnancy that resulted from in vitro fertilization should be assigned using the age of the embryo and the date of transfer. For example, for a day-5 embryo, the EDD would be 261 days from the embryo replacement date. Likewise, the EDD for a day-3 embryo would be 263 days from the embryo replacement date.

## Clinical Considerations in the Second Trimester

Using a single ultrasound examination in the second trimester to assist in determining the gestational age enables simultaneous fetal anatomic evaluation. However, the range of second-trimester gestational ages (14 0/7 weeks to 27 6/7 weeks of gestation) introduces greater variability and complexity, which can affect revision of LMP dating and assignment of a final EDD. With rare exception, if a first-trimester ultrasound examination was performed, especially one consistent with LMP dating, gestational age should not be adjusted based on a second-trimester ultrasound examination. Ultrasonography dating in the second trimester typically is based on regression formulas that incorporate variables such as

- the biparietal diameter and head circumference (measured in transverse section of the head at the level of the thalami and cavum septi pellucidi; the cerebellar hemispheres should not be visible in this scanning plane)
- the femur length (measured with full length of the bone perpendicular to the ultrasound beam, excluding the distal femoral epiphysis)
- the abdominal circumference (measured in symmetrical, transverse round section at the skin line, with visualization of the vertebrae and in a plane with visualization of the stomach, umbilical vein, and portal sinus) (8)

Other biometric variables, such as additional long bones and the transverse cerebellar diameter, also can play a role.

Gestational age assessment by ultrasonography in the first part of the second trimester (between 14 0/7 weeks and 21 6/7 weeks of gestation, inclusive) is based on a composite of fetal biometric measurements and has an accuracy of ± 7–10 days (19–22). If dating by ultrasonography performed between 14 0/7 weeks and 15 6/7 weeks of gestation (inclusive) varies from LMP dating by more than 7 days, or if ultrasonography dating between 16 0/7 weeks and 21 6/7 weeks of gestation varies by more than 10 days, the EDD should be changed to correspond with the ultrasonography dating (Table 1). Between 22 0/7 weeks and 27 6/7 weeks of gestation, ultrasonography dating has an accuracy of ± 10–14 days (19). If ultrasonography dating between 22 0/7 weeks and 27 6/7 weeks of gestation (inclusive) varies by more than 14 days from LMP dating, the EDD should be changed to correspond with the ultrasonography dating (Table 1). Date changes for smaller discrepancies (10–14 days) are appropriate based on how early in this second-trimester range the ultrasound examination was performed and on clinician assessment of LMP reliability. Of note, pregnancies without an ultrasound examination that confirms or revises the EDD before 22 0/7 weeks of gestational age should be considered suboptimally dated (see also Committee Opinion 688, *Management of Suboptimally Dated Pregnancies* [23]).

## Clinical Considerations in the Third Trimester

Gestational age assessment by ultrasonography in the third trimester (28 0/7 weeks of gestation and beyond) is the least reliable method, with an accuracy of ± 21–30 days (19, 20, 24). Because of the risk of redating

**Table 1.** Guidelines for Redating Based on Ultrasonography ⇦

| Gestational Age Range* | Method of Measurement | Discrepancy Between Ultrasound Dating and LMP Dating That Supports Redating |
|---|---|---|
| ≤13 6/7 wk | CRL | |
| • ≤ 8 6/7 wk | | More than 5 d |
| • 9 0/7 wk to 13 6/7 wk | | More than 7 d |
| 14 0/7 wk to 15 6/7 wk | BPD, HC, AC, FL | More than 7 d |
| 16 0/7 wk to 21 6/7 wk | BPD, HC, AC, FL | More than 10 d |
| 22 0/7 wk to 27 6/7 wk | BPD, HC, AC, FL | More than 14 d |
| 28 0/7 wk and beyond† | BPD, HC, AC, FL | More than 21 d |

Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; CRL, crown–rump length; FL, femur length; HC, head circumference; LMP, last menstrual period.

*Based on LMP.

†Because of the risk of redating a small fetus that may be growth restricted, management decisions based on third-trimester ultrasonography alone are especially problematic and need to be guided by careful consideration of the entire clinical picture and close surveillance.

a small fetus that may be growth restricted, management decisions based on third-trimester ultrasonography alone are especially problematic; therefore, decisions need to be guided by careful consideration of the entire clinical picture and may require close surveillance, including repeat ultrasonography, to ensure appropriate interval growth. The best available data support adjusting the EDD of a pregnancy if the first ultrasonography in the pregnancy is performed in the third trimester and suggests a discrepancy in gestational dating of more than 21 days.

## Conclusion

Accurate dating of pregnancy is important to improve outcomes and is a research and public health imperative. As soon as data from the LMP, the first accurate ultrasound examination, or both are obtained, the gestational age and the EDD should be determined, discussed with the patient, and documented clearly in the medical record. Subsequent changes to the EDD should be reserved for rare circumstances, discussed with the patient, and documented clearly in the medical record. When determined from the methods outlined in this document for estimating the due date, gestational age at delivery represents the best obstetric estimate for the purpose of clinical care and should be recorded on the birth certificate. For the purposes of research and surveillance, the best obstetric estimate, rather than estimates based on the LMP alone, should be used as the measure for gestational age. A pregnancy without an ultrasound examination that confirms or revises the EDD before 22 0/7 weeks of gestational age should be considered suboptimally dated.

The American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal–Fetal Medicine recognize the advantages of a single dating paradigm being used within and between institutions that provide obstetric care. Table 1 provides guidelines for estimating the due date based on ultrasonography and the LMP in pregnancy, and provides single-point cutoffs and ranges based on available evidence and expert opinion.

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ISSN 1074-861X

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Methods for estimating the due date. Committee Opinion No. 700. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;129:e150–4.

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Seminars in
ULTRASOUND
CT and MRI

# Is Ultrasound the New Gold Standard for the Diagnosis of Ectopic Pregnancy?

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**Ultrasound technology and in particular the use of transvaginal imaging has taken the guesswork out of ectopic pregnancy diagnosis. The vast majority of ectopic pregnancies can and should be diagnosed with a high degree of certainty before management is commenced. More and more women with ectopic pregnancy are eligible for nonsurgical intervention because ultrasound has enabled clinicians to make the diagnosis much earlier in its natural history. We believe that laparoscopy, traditionally the gold standard in diagnosis of ectopic pregnancy, should not be used in modern management. There is more and more evidence to support the use of transvaginal ultrasound as the primary diagnostic tool for ectopic pregnancy. In this review we hoped to demonstrate that transvaginal ultrasound is the new gold standard for the diagnosis of ectopic pregnancy.**
**Semin Ultrasound CT MRI 29:114-120** 

Ectopic pregnancy is still one of the most common causes of maternal death in the first trimester. In the United Kingdom, it was responsible for 73% of early pregnancy deaths according to the most recent triennial report.[1] In recent years, our ability to diagnose ectopic pregnancy much earlier in its natural history has meant that women rarely present with collapse and shock requiring emergency laparotomy. We believe that this is thanks to the introduction of high-resolution transvaginal probes, improved training in the diagnosis and management of early pregnancy complications, the rapid immunoassay of serum human chorionic gonadotrophin (hCG) levels, and an open access policy for women with vaginal bleeding or lower abdominal pain in the first trimester.[2-5] In modern management, women with ectopic pregnancy tend to be more clinically stable, have no signs of hemoperitoneum on ultrasound, and tend to have relatively low levels of serum hCG. Consequently, more conservative treatment modalities such as a "wait and watch" expectant approach or medical management with methotrexate are being offered to women with ectopic pregnancy. In this review, we will critically evaluate the role of ultrasound and in particular of transvaginal ultrasound (TVS) as the new gold standard for the diagnosis of ectopic pregnancy. We will also discuss the ultrasonographic appearances of caesarean section scar pregnancies as well as cervical pregnancies as these are increasing in prevalence.

## Where Should Women with First-Trimester Lower Abdominal Pain ± Vaginal Bleeding Be Assessed?

Ideally first-trimester women should be evaluated in dedicated early pregnancy units (EPUs). These units were introduced in the United Kingdom in order to streamline the evaluation and management of women with early pregnancy complications. They have been demonstrated to perform well in terms of cost-effectiveness and patient safety.[2,3] In EPUs, evidence-based protocols that combine ultrasound and biochemical data result in more conservative treatment modalities being applied to early diagnosed ectopic pregnancies. In expert hands, a conservative management should not only include traditional methotrexate[6] but also an expectant "wait and see" approach.[7] In an ideal world, complete management in the form of history-taking, clinical examination, ultrasound diagnosis, and management should be the benchmark standard of care for all women with early pregnancy complications and in particular ectopic pregnancy. This "one-stop"

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doi:10.1053/j.sult.2008.01.001

approach facilitates reductions in follow-up, admission rates, and occupied bed-stays.[2] TVS enables the clinician to not only confirm the viability and gestation of the pregnancy but most importantly the location of the pregnancy.

## Is Laparoscopy Still the Gold Standard?

Laparoscopy is traditionally considered the gold standard in the diagnosis of pelvic diseases, including tubal ectopic pregnancy.[8] In women with tubal ectopic pregnancy, the presence of chorionic villi in the fallopian tube at histology confirms the diagnosis. Laparoscopy is however an invasive operation which requires general anesthetic and, although major complications are very rare, they can be catastrophic. In fact, the assumption that laparoscopy has a 100% sensitivity for the detection of ectopic pregnancy is questionable. False-negative laparoscopies can occur when an ongoing ectopic pregnancy is laparoscoped too early in its development and therefore too small to be visualized at laparoscopy. When a tubal ectopic pregnancy fails spontaneously, this can also result in potentially negative laparoscopies. If there is any doubt about the location of a pregnancy and a woman is clinically stable, laparoscopy should not be used as a diagnostic tool, even if the initial serum hCG is above a particular discriminatory zone.[9] There is however growing evidence that TVS should be considered the preferred primary diagnostic tool of choice in modern practice.[4,8,9,23,24] In fact, we contest that if an extra-uterine pregnancy cannot be seen using TVS, then laparoscopy will almost certainly also be negative. Conversely if an experienced sonographer can see an extra-uterine pregnancy at TVS, it will almost certainly be present at subsequent laparoscopy. In women who require surgery for their ectopic pregnancy, one would hope that the diagnosis has already been made preoperatively using ultrasound. This invaluable preoperative information allows the surgical team to not only plan the most appropriate endoscopic procedure but also give them a mandate to appropriately counsel and consent the woman for either salpingectomy or linear salpingotomy.[14-19] TVS has been shown to be accurate and cost-effective and has no complications.[8-13] Conversely laparoscopy is an invasive procedure, not without complications, and it is difficult to justify its routine use in pregnant women for the diagnosis of ectopic pregnancy. Any unit which continues to use laparoscopy as a diagnostic tool for ectopic pregnancy needs to reevaluate its quality of early pregnancy care. We acknowledge that in women who are clinically unstable, surgery should never be delayed so that an ultrasound scan can be performed.

## Is There a Place for Transabdominal Ultrasound?

No! There is no role for the use of transabdominal sonography (TAS) as a primary investigative tool in the modern management of women with first-trimester symptomatology. ALL women with lower abdominal pain in the first trimester should have a primary TVS rather than a TAS. In the past, TAS was the first imaging technique chosen to exclude an intrauterine pregnancy. In the absence of an intrauterine pregnancy and serum hCG levels above 6500 IU/L, an ectopic pregnancy was the likely diagnosis.[20] However the diagnostic reliability of TAS has been shown to be only 70% under ideal conditions.[12] Consequently the use of the transabdominal approach should be restricted only to the cases in which the region to be imaged is beyond the maximum depth of the transvaginal probe.

Interestingly, some studies have evaluated the effectiveness of TAS in predicting the presence of significant hemoperitoneum in trauma patients seen in the Emergency Department.[21,22] A quick bedside TAS assessing Morison's pouch (the space between Glisson's capsule of the liver and Gerota's fascia of the kidney) has been shown to correlate well with significant hemoperitoneum, therefore, reducing the interval time for surgery.[21,22] In the authors' opinion, the use of TAS for women with TVS confirmed ectopic pregnancy should be limited to those women with blood in the pouch of Douglas. TAS evaluation of Morison's pouch may prove to be valuable in determining the presence of significant hemoperitoneum in the preoperative ultrasound evaluation of women with ectopic pregnancy.

## Transvaginal Ultrasound: How Reliable Today?

Today, the diagnosis of ectopic pregnancy should be based upon the positive visualization of an adnexal mass using TVS rather than the absence of an intrauterine pregnancy sac. Although many physicians would be reluctant to use TVS alone as the primary diagnostic tool for ectopic pregnancy, there is substantial evidence that this diagnosis can be made exclusively on the basis of sonographic signs. If an ectopic pregnancy is present, 87 to 93% can be identified using TVS prior to surgery.[4,8,9,23,24] It can be argued, however, that the majority of these studies have evaluated the cumulative performance of ultrasound, often after many repeated scans, prior to treatment commencement. This is an important limitation of previous published data and reflects a very good overall sensitivity.[4,8,9,23,24] The estimation of TVS accuracy in the prediction of ectopic pregnancy is very high indeed as reflected in these data.[4,8,9,23,24] In fact, none of these studies have attempted to evaluate the true sensitivity of the first TVS in women with an underlying tubal ectopic pregnancy. In addition, most of these papers tend relate to selected populations of women and some are retrospective studies.

Trying to overcome these limitations, we recently investigated the diagnostic effectiveness of the first or primary TVS in the pickup of ectopic pregnancy. In this study, we attempted to quantify the true detection rate of TVS at the first scan. This is a more realistic and reproducible scenario that gives a genuine feel for ultrasound performance at the first clinical interface.[25] In this recently published study, unselected women in an EPU population were managed accord-

**Table 1** Summary of Studies Assessing Performance of TVS to Diagnose Ectopic Pregnancy

| Source | Total *N* | Ectopic Pregnancy, *n* (%) | Type of Study | Population | Type of Diagnostic Technique | Sensitivity of Initial TVS to Diagnose EP | Overall Sensitivity to Detect EP | Overall Specificity to Detect EP | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Braffman et al. (1994)[23] | 1427 | 103 (7%) | Prospective | Women attending the Emergency Department with pain, bleeding or emesis | TAS, TVS and serum hCG levels | — | 99% | 84% | 7% (103/1427) had confirmed EP 45% women had TAS 55% women had TAS and TVS 93.7% had serum hCG level >1500 IU/l |
| Cacciatore et al. (1994)[42] | 225 | 55 (24%) | Prospective | Women at increased risk of EP | TVS and serum hCG levels | 84% | 84% | 98.8% | 24% (55/225) had confirmed EP 84% (46/55) were diagnosed on the initial TVS False-positive rate was 1.2% |
| Shalev et al. (1998)[9] | 845 | 380 (45%) | Prospective | Women with presumed EP seen in the Emergency Department | TVS and serum hCG levels | — | 87% | 94% | 45% (380/845) had confirmed EP PPV 92.5% NPV 90% |
| Atri et al. (2003)[4,a] | 143 | 143 (100%) | Retrospective | Women with surgically confirmed EP | TVS | — | 93.8% | — | Retrospective review of women with surgically confirmed EP |
| Condous et al. (2005)[5,13] | 152 | 143 (94%) | Prospective | Women undergoing surgery for EP suspected on US | TVS | — | 90.9% | 99.9% | Prospective observational study PPV 93.5% NPV 99.8% |
| This study, 2007 | 5240 | 119 (2.3%) | Prospective | Women attending the EPU | TVS | 73.9% | 98.3% | 99.9% | 2.3% (119/5240) had confirmed EP |

Reprinted with permission from Kirk et al.[25]

[a]The study was on a total of 290 women. We have included the 143 women who had TVS, but excluded the 147 women who had a suprapubic scan.

Abbreviations: TAS, transabdominal ultrasound scan; EPU, early pregnancy unit; PPV, positive predictive value; NPV, negative predictive value.

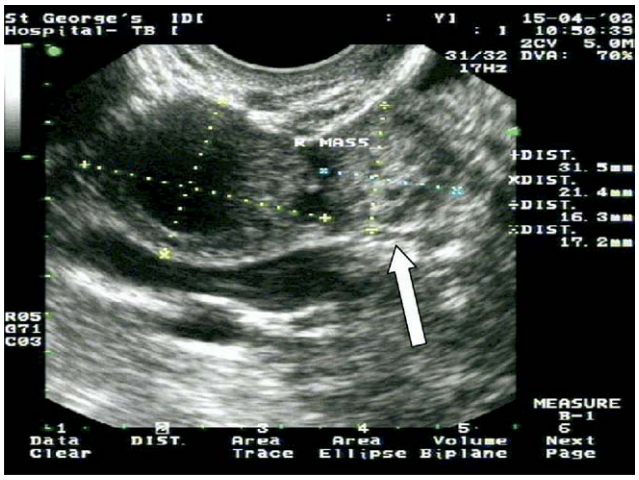


**Figure 1** Tubal ectopic pregnancy; the white arrow depicts an inhomogeneous mass or blob sign on transvaginal scan. (Reprinted with permission from Condous et al.[3]) (Color version of figure is available online.)

ing to a strict protocol. In this large population of 5240 women attending the EPU, the single initial scan detected almost 75% of all ectopic pregnancies with a high specificity of 99.9% (Table 1). The TVS identified 9% of women as having a pregnancy of unknown location (PUL) at the first scan and 6.8% of this group went on to be ectopic pregnancies at follow-up scan. If we look at the overall performance of the first and repeated ultrasound scans, the overall sensitivity of TVS in the diagnosis of ectopic pregnancies was much higher (98.3%). This is because some ectopic pregnancies subsequently visualized on TVS are initially classified as PULs. The results from this study are the first to validate the primary TVS in women with an ectopic pregnancy. This important information can be utilized by other EPUs, which to date have not published their results. This uncontested benchmark may well be undervaluing the performance of the first scan; however, only similar studies on other EPU populations will confirm or refute this figure. This study confirms that TVS in the context of an EPU can lead to an accurate diagnosis avoiding unnecessary interventions and without compromising safety. Ultrasound does not require a general anesthetic; it is not invasive, and it is a reproducible diagnostic modality. In well-trained hands, it is the most appropriate approach to the diagnosis of ectopic pregnancy.

## Ectopic Pregnancy or Pregnancy of Unknown Location?

The sonographic diagnosis of ectopic pregnancy must be made on the basis of positive ultrasound findings. In the absence of intrauterine or extra-uterine sonographic signs of pregnancy, we strongly discourage the practice of labeling these women as a "query ectopic pregnancy." This approach is not helpful and may result in unnecessary interventions and increased emotional stress for the women. When the pregnancy cannot be visualized on TVS either inside or outside the uterus, then we advocate the use of the descriptive term of "pregnancy of unknown location."[26-36] We have observed that only about 8% of the pregnancies initially diagnosed as PULs end up to be ectopic pregnancies at the subsequent follow-up.[29] This means that if we are not able to locate the pregnancy at the initial scan and the pelvis is normal, then we can counsel the patient about a relatively low risk of ectopic pregnancy and offer expectant, outpatient-based subsequent follow-up. The combined ultrasound-biochemical follow-up of PULs has been extensively covered by other articles and will not be the topic of this review.[26-36] It is very important for EPUs and scanning based units NOT to use PUL as an interchangeable term with ectopic pregnancy.

## The Criteria for the Transvaginal Ultrasound Diagnosis

We have already stressed the importance of a distinction between ectopic pregnancy and PUL. In other words, the diagnosis of ectopic pregnancy should be based upon the positive visualization of an adnexal mass at TVS rather than on the absence of an intrauterine gestational sac. In the absence of an intrauterine gestational sac on scan, a careful evaluation of both adnexa for any extra-ovarian mass is crucial, since the fallopian tubes are the most frequent site for ectopic implantation. However, which characteristics should this mass have?

The ultrasound diagnosis of an ectopic pregnancy can be made if one of the following sign is noted at the time of the early pregnancy scan: (1) an inhomogeneous mass or blob sign in the adnexal region, which is adjacent to the ovary and moving separately (Fig. 1)[13]; (2) a mass with a hyperechoic ring around the gestational sac, also described as the bagel sign (Fig. 2)[13]; (3) a gestational sac containing a fetal pole with cardiac activity (ie, a viable extra-uterine pregnancy; Fig. 3)[13]; or (4) a gestational sac containing a fetal pole with-

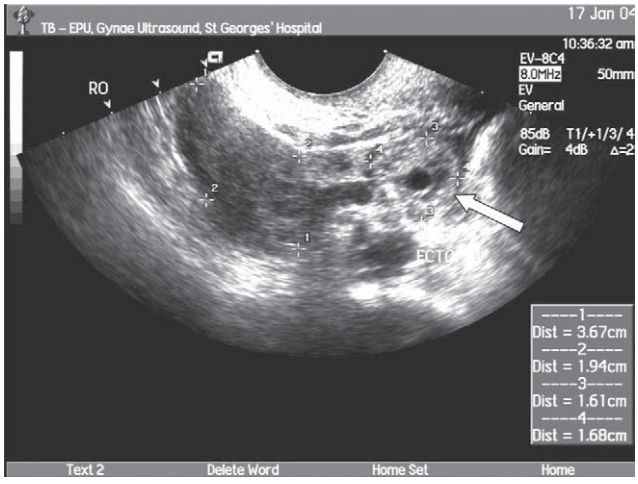


**Figure 2** Transvaginal scan image demonstrating bagel sign. The white arrow shows ectopic pregnancy characterized by the bagel sign. (Reprinted with permission from Condous et al.[3])

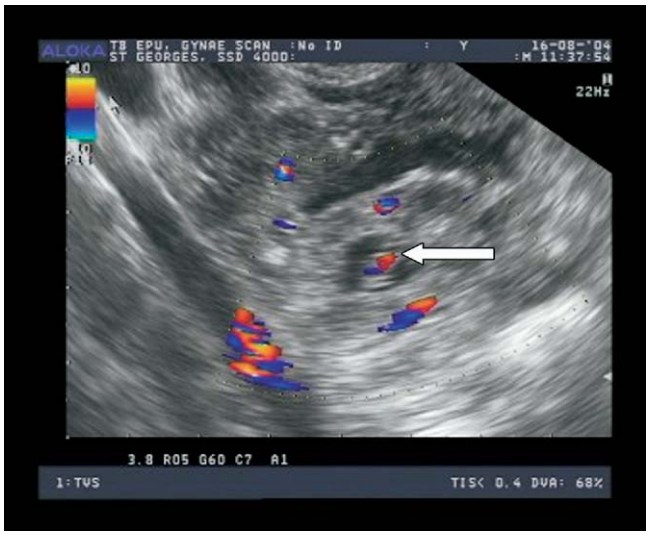


**Figure 3** Cardiac activity demonstrated with color Doppler in a viable tubal ectopic pregnancy. Solid arrow points at fetal pole. (Color version of figure is available online.)

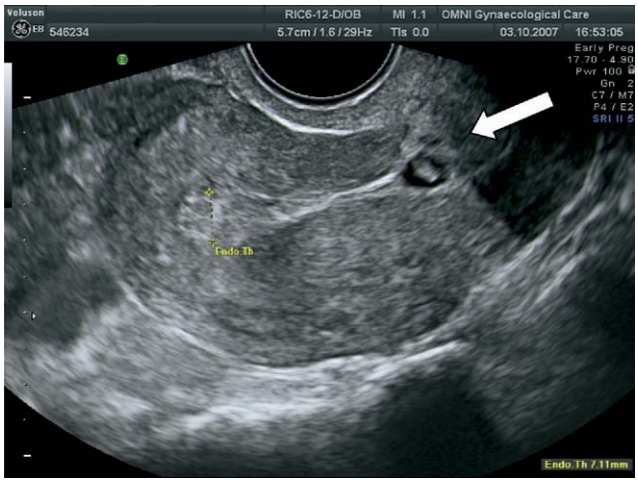


**Figure 5** Caesarean section scar pregnancy. The ectopic sac with visible fetal pole (solid arrow) is within the myometrial defect at the site of a previous caesarean section. (Color version of figure is available online.)

out cardiac activity (ie, a nonviable extra-uterine pregnancy; Fig. 4).

As a tip, it should be noted that the visualization of the corpus luteum may be helpful when looking for an ectopic pregnancy. It has been shown to be on the ipsilateral side in 70 to 85% of cases.[13,37,38] Consequently, if there is no sign of intrauterine pregnancy at the initial TVS, the clinician should try to visualize the corpus luteum first; if an ectopic pregnancy is present, it will be on the same side as this in the majority of cases.

The author's recent study[13] on the use of TVS as a preoperative diagnostic tool confirmed previous data regarding the characteristic appearances of ectopic pregnancy on TVS. The majority of confirmed ectopic pregnancies were seen as an inhomogeneous mass or blob sign (57.9%) on scan; 20.4% were visualized as a hyperechoic ring or bagel sign, and only 13.2% were visualized as gestational sac with a fetal pole (55% of these had positive fetal cardiac activity and 45% had no fetal cardiac activity). Misdiagnosis using TVS should be relatively uncommon and, in this study, the false-positive rate was 5.9%. In a meta-analysis of 10 studies involving a total of 2216 women (565 with ectopic pregnancies and 1651 without ectopic pregnancies) the performance of TVS for the diagnosis of ectopic pregnancy was evaluated.[39] Four different ultrasonographic criteria were assessed: criterion A, a gestational sac with a fetal pole with cardiac activity (ie, a viable extrauterine pregnancy; Fig. 3); criterion B, a gestational sac with a fetal pole without cardiac activity (ie, a nonviable extrauterine pregnancy; Fig. 4); criterion C, a mass with a hyperechoic ring around the gestational sac (ie, an empty tubal ring; Fig. 2); and criterion D, an inhomogeneous adnexal mass or blob sign (Fig. 1). The positive-predictive values for criteria A, B, and C were 97.8 to 100%. In conclusion, TVS, in the hands of an expert sonographer, represents a powerful and reliable diagnostic tool. It is author's hope

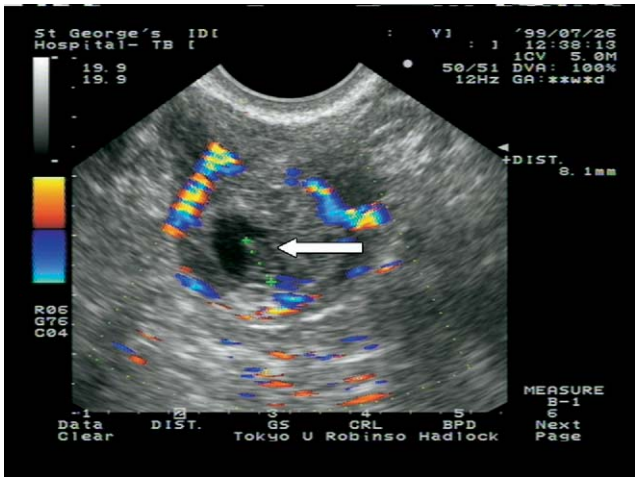


**Figure 4** Nonviable tubal ectopic pregnancy at color Doppler. Solid arrow points at fetal pole. (Color version of figure is available online.)

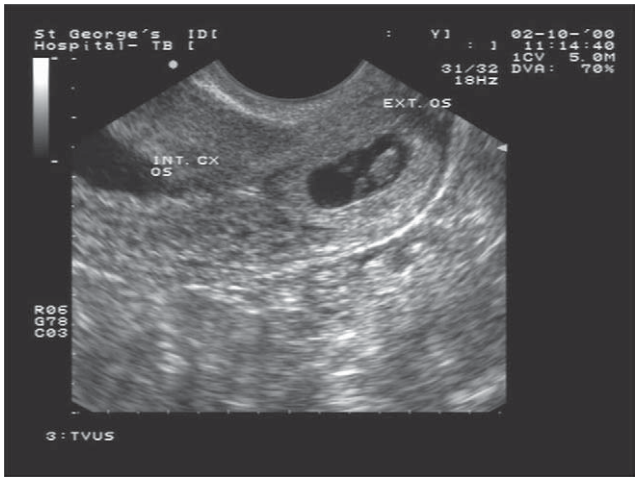


**Figure 6** Sagittal view of a cervical ectopic pregnancy. (Reprinted with permission from Condous.[3])

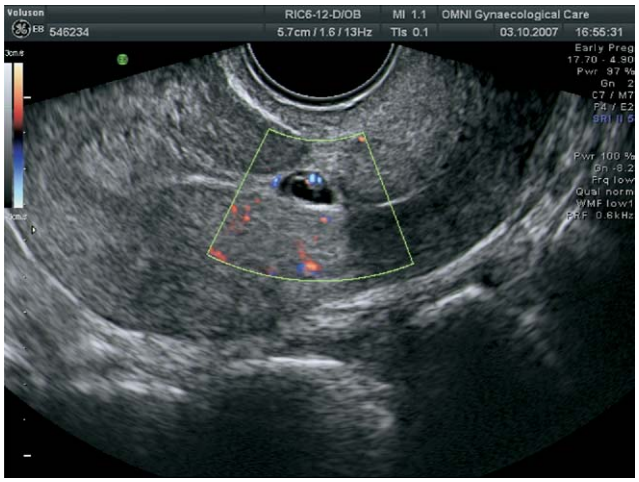


**Figure 7** Viability of a caesarean section scar pregnancy demonstrated with color Doppler. (Color version of figure is available online.)

that in the future the high predictive value of TVS could help limit the use of laparoscopy only to the treatment of those ectopic pregnancies not eligible for conservative management.

## Tips for Caesarean Section Scar and Cervical Pregnancies

Although it is still a rare entity, the incidence of caesarean section scar pregnancy over the last decade has been increasing with a current estimated incidence of 1:1800 to 1:2216 normal pregnancies.[40] More than half of the reported cases had only one prior caesarean delivery. The incidence of cervical pregnancy is about 1:10,000 normal deliveries, but the case reports of cervical heterotopic (simultaneous intrauterine and cervical pregnancies) are increasing due the wide diffusion of assisted reproductive techniques.[41]

In the caesarean section scar pregnancy group, the gestational sac is visualized within a clear myometrial defect at the site of a previous caesarean section (Fig. 5). In the cervical pregnancy group, the sac is located in the endocervical canal below the level of the internal os (Fig. 6). Whenever a gestational sac is visualized in the cervico-isthmic region of the uterus, it is crucial to differentiate it from the cervical passage of an intrauterine pregnancy which is miscarrying. Applying gentle pressure with the probe can be helpful: if we are able to displace the gestational sac from its position within the endocervical canal or very near to the previous caesarean section scar, the so-called "sliding organs" sign, then it is more likely to be a miscarriage rather than an implanted cervical pregnancy or caesarean section scar pregnancy. Also the absence of trophoblastic circulation around the sac using color Doppler means that the pregnancy sac is passing through the lower uterine cavity/endocervical canal rather than being implanted at the site (Fig. 7).

## Conclusions

Ultrasound, and in particular TVS, is the new gold standard for the diagnosis of ectopic pregnancy. TVS is a noninvasive, highly reproducible diagnostic tool which is well accepted by women with first-trimester complications. Laparoscopy should not be used as diagnostic tool in the workup of women with ectopic pregnancy. The introduction of TVS has not only had an impact on maternal morbidity and mortality figures but also facilitated greater management options, ie, conservative approaches to ectopic pregnancy care. We should not be fixated with the preoperative diagnostic performance of TVS—its invaluable benefits in accurately diagnosing ectopic pregnancy are well documented. Instead we should focus our attention on managing ectopic pregnancies more conservatively. This will require a concerted effort not only in ultrasound training but also acknowledging that ectopic pregnancy management requires specialist input in order to optimize clinical outcomes.

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The Danco Group

January 21, 2000

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-687, Mifepristone 200mg Oral Tablets**
- Amendment 039 - Mifeprex® – Distribution Plan

Dear

As previously agreed, we are submitting Danco Laboratories, Inc.'s Distribution Plan for Mifeprex®. This is a comprehensive distribution plan that emphasizes control of mifepristone at all points in the supply chain, from manufacturers through to individual patients. This plan has been prepared in light of the unique situation surrounding abortion provision in the United States and not out of any medical safety concerns. However, in preparation of this plan, we have taken into account advice from the FDA that it is considering approving the NDA under "Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, Sec. 314.520--Approval with restrictions to assure safe use."

Our position is that we are willing to agree with the FDA on appropriate distribution controls for mifepristone but that the application of Sec. 314.520 under Subpart H seems unnecessary, in light of our voluntary acceptance of some appropriate distribution controls.

Specifically, Sec. 314.520(a) states that the FDA can apply post-marketing restrictions if it "concludes that a drug product shown to be effective can be safely used *only* if distribution or use is restricted" (emphasis added). Regardless of the distribution system for mifepristone, the medical safety of this drug is well documented in our IND application and in the label and, thus, we believe that Sec. 314.520 does not apply.

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is

On the contrary, scientific evidence demonstrates that mifepristone is an exceptionally safe drug. Mifepristone when taken by a woman whose pregnancy is ≤ 49 days LMP is associated with several relatively minor and predictable side effects. More serious adverse events are quite rare and are related to the entire treatment (not mifepristone *per se*), almost always following the use of the prostaglandin. There has never been a death related to the use of mifepristone in combination with misoprostol for medical termination of pregnancy. These details have been discussed and reported in our label and various submissions to the FDA.

In addition to concerns about patient safety, the possibility of teratogenic effects has previously triggered the application of section 314.520, as in the case of Thalomid (Thalidomide). These concerns relate to the inadvertent use of a known teratogen at the early stages of a pregnancy that was not scheduled for termination. In contrast, all women who will receive mifepristone will be known to be in early pregnancy and have elected to terminate that pregnancy. Of course, in the case of a successful application of mifepristone, concerns about teratogenicity are rendered moot as the woman will no longer be pregnant. Similarly, in the case of a failed medical abortion, women should have a surgical intervention to terminate the pregnancy and are counseled to do so before taking mifepristone and misoprostol. To date, there is no compelling evidence to suggest that either mifepristone or misoprostol produces teratogenic effects.

Based on the above reasons, we firmly believe that the NDA for mifepristone should not be approved under Sec. 314.520. In addition, applying Sec. 314.520 might draw increased and unwarranted attention to the product, the FDA, and to Danco and its manufacturers, in particular evoking queries about the product's safety. Nonetheless, given the contentious political climate surrounding *all* abortion provision in the United States, we feel that the distribution of mifepristone should be carefully monitored and controlled. Therefore, we have developed and are implementing a controlled distribution strategy and are submitting the details of this strategy in the enclosed Distribution Plan for your review and comment.

Sincerely,

/S/

President and Chief Executive Officer

/dns
Enclosure

cc: [redacted]
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

[redacted]

# MIFEPREX®

# DISTRIBUTION PLAN

## January 21, 2000

# MIFEPREX®

## DISTRIBUTION PLAN

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# MIFEPREX®

## DISTRIBUTION PLAN

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# MIFEPREX®

## DISTRIBUTION PLAN

## EXECUTIVE SUMMARY

This Distribution Plan for Mifeprex® demonstrates Danco Laboratories Inc.'s ("Danco") commitment to distributing Mifeprex® safely and efficiently while, at the same time, providing needed services and information to providers and patients in a confidential manner. Danco has a keen awareness of and sensitivity to the regulatory requirements, as well as the market and political dynamics, surrounding introduction of Mifeprex® in the United States. Therefore, Danco has established a **controlled distribution strategy** to best meet the goals of safe, efficient and confidential distribution of Mifeprex®.

This strategy ensures that Danco exerts positive control over distribution of Mifeprex® through all phases of manufacturing, storage, shipment and administration from manufacturer to patient. Key control elements throughout the distribution process include the following:

- Secure manufacturing, receiving and holding areas for Mifeprex®
- Secure shipping procedures, including tamper-proof seals
- Controlled returns procedures
- Tracking system ability to trace individual packages to patient level, while maintaining patient confidentiality
- Use of only [redacted] authorized distributors and a logistics partner, all of whom have necessary expertise, capabilities and industry experience to handle distribution requirements for Mifeprex®
- Required Account Registration and Order Form signed by providers, prior to any Mifeprex® order being shipped
- Mifeprex® availability only to registered providers, not through retail pharmacies
- Documented patient acknowledgment (informed consent), signed by patient and provider

Alongside key control elements, Danco also recognizes the need to provide support and access to training, services and information throughout the supply chain. The support that is built into the distribution system is as follows:

Access to multi-media training materials and training programs with continuing medical education (CME) recognition and credits.

- Danco toll-free telephone information network for consumers and providers, with access to medical consultants for providers' medical questions
- Danco web site information network
- Trained service representatives for distributors' questions through the logistics partner

Danco has developed and assembled the infrastructure to ensure that Danco's goal of safe, efficient and confidential distribution of Mifeprex® is attained. The Distribution Plan for Mifeprex® details Danco's controlled distribution strategy, highlighting key control elements at each point in the supply chain.

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The Heritage Foundation

LEGAL MEMORANDUM

No. 324 | FEBRUARY 8, 2023

EDWIN MEESE III CENTER FOR LEGAL & JUDICIAL STUDIES

# The Justice Department Is Wrong: Federal Law Does Prohibit Mailing Abortion Drugs

*Thomas Jipping and Sarah Parshall Perry*

**KEY TAKEAWAYS**

Federal law has prohibited mailing abortion drugs for more than 100 years.

The Justice Department bypassed the statutory interpretation rules to invent a version of the Comstock Act that would not hinder abortion access.

Congress has repeatedly chosen to maintain the Comstock Act's plain language, which clearly prohibits mailing abortion drugs.

First under English common law, then under American statutes, an "unbroken tradition of prohibiting abortion on pain of criminal punishment"[1] began more than seven centuries ago.[2] By 1868, "a supermajority of States (at least 26 of 37) had enacted statutes criminalizing abortion at all stages of pregnancy."[3]

Five years later, in 1873, in the middle of this national pro-life legislative movement, Congress enacted a statute with an ambitious title: *An Act for the Suppression of Trade in, and Circulation of, Obscene Literature and Articles of Immoral Use*.[4] It is often referred to as the Comstock Act after Anthony Comstock, the anti-vice crusader who championed its passage and spent more than 40 years enforcing it as a U.S. Postal Service special agent.[5] Section 2 of the Comstock Act appears today as 18 U.S.C. § 1461, prohibiting the Postal Service from delivering, and anyone from "knowingly" using the mail to send, any "article or thing designed, adapted, or intended for producing abortion."[6]

This provision could not, as a practical matter, be enforced while the Supreme Court's decisions in *Roe v. Wade*[7] and *Planned Parenthood v. Casey*,[8] which invented and subsequently affirmed a constitutional right to abortion, remained operative precedents. That blockade lifted on June 24, 2022, when the Supreme Court in *Dobbs v. Jackson Women's Health Organization* overruled *Roe* and *Casey*, holding that "the Constitution does not confer a right to abortion."[9]

One week later, the Postal Service's general counsel asked the Department of Justice's Office of Legal Counsel (OLC)[10] whether § 1461 "prohibits the mailing of mifepristone and misoprostol, two prescription drugs that are commonly used to produce abortions."[11] In a written opinion dated December 23, 2022, the OLC concluded that "section 1461 does not prohibit the mailing, or the delivery or receipt by mail, of mifepristone or misoprostol *where the sender lacks the intent that the recipient of the drugs will use them unlawfully*."[12]

The Postal Service should not see this as good news. The OLC did not explore the additional responsibilities that its interpretation of § 1461 would impose upon the Postal Service. On its face, however, that interpretation means that, to know whether it may handle a particular mailing of abortion drugs, the Postal Service must identify its "sender" and ascertain his or her specific intent regarding unlawful use by the "recipient." Neither the original Comstock Act, nor § 1461 today, however, mentions any "sender" or "recipient," and the OLC opinion makes no attempt to define these important new terms. The opinion nonetheless concedes that "those sending or delivering mifepristone and misoprostol typically will lack complete knowledge of how the recipients intend to use them and whether that use is unlawful under relevant law."[13]

The OLC has, therefore, effectively created a new statute, intentionally neutralizing the current one so that it poses no obstacle to the Biden Administration's agenda of maximizing abortion access. This exercise cannot be called "interpretation" of an existing statute enacted by Congress.[14] This *Legal Memorandum* does what the OLC chose not to do, following the established process of statutory interpretation to properly answer the Postal Service's question.

## The Comstock Act

The OLC opinion's version of § 1461 is incompatible with both the context in which the Comstock Act was first enacted and its subsequent legislative development.

**Context for the Comstock Act.** Writing in 1958, Professor Glanville Williams, a widely acclaimed criminal law scholar law and an advocate of legalized abortion, acknowledged that American physicians led a 19th-century campaign against abortion "primarily because they believed unborn children must not be sacrificed unless the life of the mother was truly at stake."[15] Indeed, a century earlier at its May 1859 convention, the American Medical Association unanimously adopted a resolution condemning the "slaughter of countless children" and calling for laws prohibiting abortion, "at every period of gestation," except when necessary to save the mother's life.[16]

State legislatures and courts followed the physicians' lead, abandoning outdated concepts such as quickening, which recognized the unborn child as a living being only after its movement in the womb could be discerned.[17] As a result, during the 19th century, "the vast majority of the States enacted criminal statutes criminalizing abortion at all stages of pregnancy."[18] Congress enacted the Comstock Act (the Act) in this cultural and legal context.

In *Bours v. United States*, which reversed a Comstock Act conviction because of the indictment's wording, the U.S. Court of Appeals for the Seventh Circuit observed that including abortion in the original statute "indicates a national policy of discountenancing abortion as inimical to the national life."[19] In other words, the Comstock Act was Congress' contribution to the national movement toward prohibiting what the American Medical Association had called the "unwarrantable destruction of human life."[20]

This context, which the OLC completely ignored, is important because requiring proof, beyond a reasonable doubt no less, that the sender intends the recipient to use abortion drugs unlawfully virtually neutralizes the Comstock Act's application to abortion drugs. In other words, the OLC posits that Congress, at the urging of a well-known anti-vice crusader and in the middle of a national movement to prohibit abortion, enacted a statute that could not be enforced regarding abortion. That position is simply implausible on its face.

**Legislative Development of the Comstock Act.** Congress first prohibited the importation of obscene material in 1842 and, in the 1865 Post Office Act, prohibited using the "mails of the United States" to deliver an "obscene book, pamphlet, picture, print, or other publication of a vulgar and indecent character."[21] The Comstock Act soon followed. As first enacted, it prohibited only "materials relating to abortion and contraception from the mails; ordinary obscene publications slipped through the legislative net."[22] Congress quickly stepped in, expanding the statute's reach in 1876 to also include any written material "of an indecent character."[23]

As amended, § 1 of the Comstock Act directly prohibited such written materials and "any article whatever...for causing unlawful abortion" in any "place within the exclusive jurisdiction of the United States." Section 2 prohibited using the mail to deliver such materials elsewhere, and § 3 prohibited "all persons" from importing them into the United States.[24] After the Act's passage, Comstock was appointed a special agent of the U.S. Post Office with the express power to enforce the statute.[25] Two dozen states enacted their own version of the Comstock Act, some with provisions even harsher than the federal statute.[26]

In February 1878, groups led by the Liberal League presented a petition with some 70,000 signatures to Congress calling for the Act's repeal.[27] Later that year, however, the Supreme Court held that Congress' power to "establish post-offices and post-roads"[28] includes "the right to determine what shall be excluded"[29] from the mail. After a House committee hearing and recommendation, Congress left the Comstock Act unchanged.[30]

Each of Congress' subsequent amendments to the Comstock Act expanded its coverage and severity. In 1948, for example, Congress recodified the Act as 18 U.S.C. § 1461[31] and expanded it by adding "filthy" to "obscene, lewd, or lascivious" and three additional categories of written materials to which those descriptors applied. It also added "adapted" to "designed or intended" to describe the "article[s] or thing[s]" for producing abortion that could not be sent through the mail. Congress went further in 1955, adding the descriptor "vile" to the written materials that could not be sent through the mail[32] and, in 1958, doubled the fine for more than one violation of § 1461.[33]

The Comstock Act's context and overall legislative development point toward harsher penalties and broader application of its prohibitions on both written material and anything that can be used to produce abortion. In addition to the context in which the Act was passed, this legislative development makes the OLC's unusually narrow interpretation even more suspect. Turning to a more specific interpretive analysis of § 1461 further reveals the serious flaws in the OLC opinion.

## Interpreting Section 1461

The OLC opinion appears so driven by the goal of eliminating § 1461 as an obstacle to the Biden Administration's abortion agenda that it simply bypassed the established process of statutory interpretation altogether. Instead, it immediately looked outside the statute for any basis for its pre-determined conclusion.

**What the OLC Did Not Do.** The OLC opinion did not even acknowledge, let alone follow, the well-established process of statutory interpretation, which is founded on the Constitution's grant of "All legislative Powers"[34] to Congress. Interpreting any written document involves "discovering...the meaning which the authors...designed it to convey to others."[35] Applied to one of Congress's statutes, interpretation requires "adhering to *Congress's* intended meaning."[36] The Supreme Court has identified principles, or canons, that help keep interpretation focused on that necessary objective.

Three of those interpretive canons are especially relevant here:

1. "In determining the meaning of a statutory provision, 'we look first to its language, giving the words used their ordinary meaning.'"[37]

2. "Absent any textual qualification, we presume the operative language means what it appears to mean."[38]

3. "[W]here...the words of the statute are unambiguous," the "judicial inquiry is complete."[39] In that case, a court "may not resort to extrinsic evidence to interpret them."[40]

If an argument existed that Congress intended the Comstock Act, either as originally enacted or as § 1461 today, to require proof of intended unlawful use, the OLC would surely have made it. If § 1461's text was even arguably ambiguous, justifying resort to extrinsic evidence of its meaning, the OLC would have made the case. The OLC opinion, however, did neither of these, failing to even mention either the obligation to determine what *Congress* intended § 1461 to mean or any of the principles necessary for meeting that obligation. In fact, the key terms at the heart of these interpretive principles—such as "plain," "ordinary," "ambiguous," or "ambiguity"—do not appear a single time in the entire OLC opinion. Instead, the OLC opinion simply bypassed the statutory interpretation process altogether.

**What the OLC Should Have Done.** In *Marbury v. Madison*, the Supreme Court held in 1803 that "[i]t is emphatically the province and duty of the judicial department to say what the law *is*."[41] A statute, the Court has repeatedly affirmed, "is" the meaning of its text at the time the legislature enacted it. Put simply, construing a statute requires determining what the legislature meant by what it enacted. The OLC opinion, therefore, should have begun by acknowledging its obligation to "adher[e] to Congress's intended meaning" for § 1461.

Keeping this necessary goal in mind, the OLC opinion should have then applied the interpretive canons noted above to determine whether, given its plain and ordinary meaning, the text of § 1461 remains sufficiently ambiguous to warrant reliance on extrinsic evidence for its meaning. "Absent any textual qualification," the Supreme Court has held, "we presume the operative language means what it appears to mean."[42] In fact, the Court has explained, "[i]n interpreting a statute a court should always turn first to one, cardinal canon before all others. We have stated time and again that courts must presume that a legislature says in a statute what it means and means in a statute what it says there.... *When the words of a statute are unambiguous, then, this first canon is also the last: 'judicial inquiry is complete.'*"[43]

Consistent with its original title, the text of § 1461 is focused squarely on "article[s] or thing[s]" that can be used for "immoral purposes" such as abortion. It says nothing about either senders and their subjective intent or recipients and their speculated use. It simply prohibits from the mail any "*article or thing* designed, adapted, or intended for producing abortion."

Similarly, neither the original Comstock Act nor § 1461 has ever been limited to articles or things that are designed, adapted, or intended *only* for abortion. Beginning with its title, the OLC opinion actually confirms this, addressing "prescription drugs that *can* be used for abortion."[44] The fact that mifepristone and misoprostol may have other uses, therefore, is irrelevant and does not make the text of § 1461 ambiguous.

Merriam-Webster defines *design* and *intend* to mean "have as a purpose" and *adapted* as "suited by...design to a particular use."[45] The plain and ordinary meaning of § 1461 is that if abortion is a purpose for which an article or thing is suited, it may not be conveyed or delivered through the mail. Since this unambiguous meaning of these terms is plain on its face, "a court may not resort to extrinsic evidence to interpret them."[46]

The Postal Service itself takes the same approach, prohibiting items because of how they can be used rather than speculating about senders and recipients. The U.S. Postal Inspection Service's website, for example, lists various "items and substances [that] should never enter the mail system."[47] These include anything that contains mercury, household products that contain aerosol, and even lithium batteries. How these items might be used by others, or whether that use is legal or illegal, has nothing to do with labeling them as "non-mailable," the same term that appears in § 1461. In fact, the term "unlawful" does not appear on this website at all. Designating an item as non-mailable is based solely on a judgment that the item, *in and of itself*, is potentially harmful. The same is true about any "article or thing designed, adapted, or intended for producing abortion."[48]

The obvious answer to the Postal Service's question, therefore, is that yes, § 1461 prohibits mailing abortion drugs.

**The OLC's Opinion.** The OLC opinion did not do any of that. It never acknowledged its duty to adhere to Congress' intended meaning or mentioned any of the necessary statutory interpretation principles. This includes even the canon that the Supreme Court has held takes precedence "before all others," the presumption that Congress "means in a statute what it enacts there." Rather than attempt to draw Congress's intended meaning *from* § 1461, or to satisfy the prerequisite of finding ambiguity for relying on extrinsic evidence, the OLC started by searching outside the statute for a preferred meaning to impose *upon* it.

The OLC found what it was looking for in a "*judicial* construction of the Comstock Act,"[49] a few U.S. Court of Appeals decisions that appeared to interpret the Comstock Act narrowly. Since the judiciary has no power to legislate, however, the OLC still needed to somehow connect this interpretation to Congress. The OLC's theory is that, because Congress did not "disapprov[e] of the [judicial] interpretation"[50] after it was "brought to Congress's attention,"[51] Congress necessarily "ratified"[52] or "accept[ed] that narrowing construction."[53] In other words, while Congress had to act for § 1461 to exist at all, the statute could be effectively, and significantly, amended by the judiciary while Congress did nothing.

*One Note and One Statement.* The interpretation that OLC prefers, it says, was "brought to Congress's attention" in two ways. First, a "Historical and Revision Note" found in a 1945 House committee report "'invited' the 'attention of Congress'" to appeals court decisions narrowly interpreting § 1461.[54] Such notes, the OLC explains, "were written by a staff of experts hired by Congress to revise the U.S. Code in the 1940s, including the editorial staffs of the West and Thompson publishing companies."[55] Second, a statement by the Postmaster General found in a 1970 committee report explained that the Postal Service had administratively "accepted the courts' narrowing construction of the [Comstock] Act."[56]

The OLC contends, in other words, that one note and one statement by non-legislative parties, appearing in committee reports 25 years apart, were so powerful that only Congress's explicit "disapprov[al] of that interpretation"[57] could prevent the resulting transformation of § 1461. This theory is inconsistent not only with the Constitution's grant of legislative power to Congress, but with the very authority the OLC cites for this approach: *Texas Dept. of Housing and Community Affairs v. The Inclusive Housing Project, Inc.*[58]

*Texas Dept. of Housing*. In that case, a nonprofit organization that assists low-income families in finding affordable housing sued the Texas housing agency under the federal Fair Housing Act (FHA). The group claimed that the agency's pattern of allocating housing tax credits had a disparate racial impact. The Supreme Court had to decide whether § 804 of the FHA, which prohibited housing discrimination based on "race, color, religion, or national origin,"[59] should be interpreted as allowing not only suits for disparate *treatment*, but also for disparate *impact*.

The Court held that Congress "ratified the unanimous holdings of the Courts of Appeals finding disparate-impact liability"[60] when it amended the FHA in 1988 but retained § 804's existing language. That much of *Texas Dept. of Housing* appears supportive of how the OLC today wants to treat § 1461. There is a reason, however, why the OLC only cited—but did not discuss—this precedent. If *Texas Dept. of Housing* is instructive, as the OLC apparently thinks it is, then it establishes a standard for congressional ratification of a judicial construction that the OLC cannot possibly meet with respect to § 1461.

1. The Supreme Court had previously interpreted language to allow disparate-impact suits in two civil rights statutes that are "equivalent in function and purpose" to § 804.[61]

2. By 1988, "all nine Courts of Appeals to have addressed the question had concluded the Fair Housing Act encompassed disparate-impact claims,"[62] six of them in the previous six years.

3. Congress affirmatively demonstrated its "aware[ness] of this unanimous precedent"[63] by the same actions, such as committee hearings and floor speeches, that it takes when enacting or amending legislation.

4. Congress rejected a proposed amendment that would have eliminated disparate-impact liability.[64]

These factors support the Supreme Court describing Congress as making a "considered judgment"[65] to retain the previous language of § 804 while accepting that it would be interpreted, going forward, as allowing disparate-impact suits. None of these factors, however, exist regarding § 1461. The Supreme Court has never interpreted § 1461[66] or any comparable or equivalent statute to require proof of intended unlawful use. Far from the unanimous, and recent, interpretation of § 804 of the FHA, the OLC opinion cites appeals court decisions in four circuits during nearly 30 years.

More importantly, while Congress' actions regarding § 804 demonstrated its actual awareness and considered acceptance of the statute's judicial construction, § 1461's legislative development described above points in the opposite direction.

*First*, § 1 of the original Comstock Act prohibited "any drug or medicine, or any article whatever...for causing *unlawful* abortion." In contrast, § 2, which would later become § 1461, prohibited "any article or thing designed or intended for the...procuring of abortion," without the "unlawful" qualifier that the OLC today wants to impose. This distinction makes a very real difference. The Supreme Court has held that "where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion."[67] In other words, including "unlawful" in § 1 turns its absence from § 2 into an exclusion.

*Second*, this same principle applies between separate, but closely related, statutes.[68] The Tariff Act, for example, prohibits "importing into the United States from any foreign country...any drug or medicine or any article whatever for causing *unlawful* abortion."[69] The OLC opinion itself,[70] and appeals court decisions on which it relies,[71] note the difference in language between the Tariff and Comstock Acts but ignores the obvious implication that Congress, therefore, intended to exclude the "unlawful" qualifier from the latter.

*Third*, recodifying the federal criminal code in 1948[72] would have been the opportunity to add the "unlawful" qualifier to § 2 of the Comstock Act, which became § 1461. Instead, Congress repealed § 1, which contained the "unlawful" qualifier, and kept § 2, which did not.

*Fourth*, following the Supreme Court's decision in *Griswold v. Connecticut*,[73] which invented a constitutional right to use contraception, Congress in 1971 amended statutes such as § 1461 and the Tariff Act to remove their application to contraception.[74] Congress, however, did not do the same after the Supreme Court's decision in *Roe v. Wade*, retaining unchanged § 1461's application to "[e]very article or thing designed, adapted, or intended for producing abortion."

*Fifth*, on multiple occasions, Congress has considered, but has never adopted, amendments to § 1461 that would bring its text in line with the OLC's interpretation. Even suggesting such a change, of course, makes no sense if, as the OLC today claims, Congress had already ratified and accepted such a narrow interpretation. Congress' own actions show that it had not. For example:

- In 1978, when again recodifying the federal criminal code, Congress considered but did not adopt an amendment to § 1461 that would limit its application to "[e]very...drug, medicine, article, or thing *intended by the [sender]...to be used to produce illegal abortion*."[75] The House committee report confirmed that this would require "proof that the offender specifically intended that the mailed materials be used to produce an illegal abortion" under state law.[76]

- In 1996 and 1997, respectively, Representatives Patricia Schroeder (D–CO) and Barney Frank (D–MA) introduced legislation to drastically narrow the definition of "nonmailable matter" in § 1461, including eliminating any reference to abortion.[77] Neither bill, however, even had a Senate counterpart, and Congress took no action on either one.[78] As explained above, Congress including "unlawful" in § 1 of the Comstock Act and in similar statutes such as the Tariff Act created a presumption that Congress intended to exclude that element from § 2. Congress repeatedly passing up opportunities to insert a requirement of proving intended unlawful use means that nothing has rebutted that presumption.

Congress took none of the actions that, under *Texas Dept. of Housing*, would have evidenced its acceptance of the narrow judicial interpretation of § 1461 that the OLC favors. Quite the contrary. In at least these five different ways, Congress demonstrated the opposite, that it meant what it enacted in § 1461. Congress' "intended meaning" is what the statute's plain language has said from the beginning—that anything designed, adapted, or intended for producing abortion may not be sent through the mail.

Finally, the OLC opinion is problematic even on its own terms. Whether mailing abortion drugs is permissible under the OLC's preferred interpretation of § 1461 depends on whether their intended use is unlawful, which is determined by state law. The first appeals court decision cited in the OLC opinion, however, contradicts this position. In *Bours v. United States*,[79] the court held that in applying the Comstock Act "to an alleged offensive use of the mails...it is immaterial what the local statutory definition of abortion is, what acts of abortion are included, or what excluded. So the word 'abortion' in the national statute must be taken in its general medical sense."[80] The prohibition on using the mail to deliver abortion drugs, therefore, is not conditioned on the intent of the sender, the anticipated use by the recipient, or the legality of abortion in a particular state.

## Conclusion

The U.S. Postal Service asked the Justice Department's Office of Legal Counsel whether 18 U.S.C. § 1461 prohibits mailing abortion drugs. Properly answering this question requires following the established process of statutory interpretation, including principles that help maintain the priority of "adhering to Congress's intended meaning."[81] Because this process inexorably provides an affirmative answer to the Postal Service's question, the OLC avoided it altogether. Instead, the OLC immediately looked outside the statute—and outside Congress altogether—to support the answer it wanted.

The Comstock Act's purpose was "to prevent the mails from being used to corrupt the public morals."[82] The context in which it was enacted and its legislative development both show that abortion was assuredly in this category. The evidence that the OLC completely ignored shows that Congress not only never limited § 1461's application to abortion, but actually intended that this application remain unchanged.

The plain, ordinary, and unambiguous meaning of § 1461 prohibits using the mail to send or deliver anything that is designed, adapted, or intended to produce abortion. The U.S. Food and Drug Administration has confirmed that mifepristone and misoprostol are in this category, approving their use for "termination of pregnancy through 10 weeks gestation."[83] The OLC opinion itself, in its opening paragraph, does the same by describing mifepristone and misoprostol as "drugs that are commonly used to produce abortions."[84] Planned Parenthood simply calls mifepristone the "abortion pill."[85] These drugs unquestionably fall within § 1461's prohibition.

Unfortunately, the Biden Administration's political priority of expanding abortion access compromised the OLC's duty to provide objective and unbiased legal analysis. As a result, the OLC wants Americans to believe that a law enacted as part of the national pro-life legislative movement and championed by an aggressive and uncompromising anti-vice crusader is today, with no change in its language, entirely unenforceable for its intended purpose. The OLC wants Americans to ignore what they can read for themselves, that the statute has clear and unqualified language, and that Congress repeatedly demonstrated its intention to keep it that way. The OLC wants Americans to believe that while enacting the Comstock Act required Congress to act, rendering it inert and unenforceable could be accomplished by Congress failing to act at all.

The Justice Department is wrong. Federal law prohibits mailing abortion drugs.

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## Endnotes

1. Dobbs v. Jackson Women's Health Organization, 142 S.Ct. 2228, 2253 (2022).
2. *See id.* at 2249–54.
3. *Id.* at 2261.
4. 17 Stat. 598 (1873).
5. *See* Margaret A. Blanchard, *The American Urge to Censor: Freedom of Expression Versus the Desire to Sanitize Society—From Anthony Comstock to 2 Live Crew*, 33 William & Mary L. Rev. 741, 744–60 (1992). Comstock claimed that he successfully prosecuted more than 3,600 defendants and destroyed more than 160 tons of obscene literature in his role as a special agent with the U.S. Postal Service. *See* Comstock Law of (1873), JRank, https://law.jrank.org/pages/5508/Comstock-Law-1873.html#ixzz7qmkxsQb4.
6. 18 U.S.C. § 1461.
7. 410 U.S. 113 (1973).
8. 505 U.S. 833 (1992).
9. *Dobbs*, 142 S.Ct. at 2279.
10. The Office of Legal Counsel provides "written opinions and other advice in response to requests from the Counsel to the President, the various agencies of the Executive Branch, and other components of the Department of Justice." *Office of Legal Counsel*, U.S. Dep't of Just., https://www.justice.gov/olc.
11. Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortion, O.L.C. Slip Op., at 1 (Dec. 23, 2022), https://www.justice.gov/olc/opinion/file/1560596/download.
12. *Id.* (emphasis added).
13. *Id.* at 17.
14. Instead, it does what Justice George Sutherland once warned against, amending § 1461 "under the guise of interpretation." West Coast Hotel Co. v. Parrish, 300 U.S. 379, 404 (1937) (Sutherland, J., dissenting).
15. Glanville Williams, The Sanctity of Life and the Criminal Law 141 (1958).
16. Frederick N. Dyer, The Physicians' Crusade Against Abortion 76 (1999).
17. *See, e.g.*, Lamb v. State, 10 A. 208 (Md. 1887).
18. *Dobbs*, 142 S.Ct. at 2252.
19. Bours v. United States, 229 F. 960, 964 (7th Cir., 1915).
20. See Dyer, *supra* note 16.
21. 13 Stat. 504, 507 (1865). See Blanchard, *supra* note 5, at 745–46.
22. Blanchard, *supra* note 5, at 749.
23. *Id.*
24. *Id.* at 746.
25. *Id.* at 748.
26. Comstock Law of (1873), *supra* note 5. *See also* Blanchard, *supra* note 5, at 751.
27. Blanchard, *supra* note 5, at 752.
28. U.S. Const., art. I, § 8, cl. 7.
29. Ex parte Jackson, 96 U.S. 727, 732 (1878).
30. Blanchard, *supra* note 5, at 754.
31. 62 Stat. 768 (1948), ch. 645.
32. Pub. L. 95–190, 69 Stat. 183 (1955).
33. Pub. L. 85–796, 62 Stat. 768 (1958).
34. U.S. Const., art I, § 1.
35. Black's Law Dictionary 824 (7th ed. 1999).
36. Valerie C. Brannon, Cong. Rsch. Srvc., R45153, Statutory Interpretation, Theories, Tools, and Trends 2 (2022) (emphasis added).

37. Lawson v. FMR LLC, 571 U.S. 429, 440 (2014), quoting Moskal v. United States, 498 U.S. 103, 108 (1990).
38. *Id.* at 441.
39. Desert Place, Inc. v. Costa, 539 U.S. 90, 99 (2003) (internal citations omitted). *See also* Babb v. Wilkie, 140 S.Ct. 1168, 1177 (2020); Lawson v. FMR LLC, 571 U.S. 429, 440 (2014), quoting *Moskal*.
40. Coast Fed. Bank, FSB v. United States, 323 F.3d 1035, 1040 (Fed. Cir. 2003) (en banc). *See also* Steimel v. Wernert, 823 F.3d 902, 912 (7th Cir. 2016).
41. Marbury v. Madison, 5 U.S. 137, 177 (1803) (emphasis added).
42. *Id.* at 441.
43. Connecticut Nat'l Bank v. Germain, 503 U.S. 249, 253–54 (1992) (emphasis added), quoting Rubin, 449 U.S. 424 (1981), at 430.
44. O.L.C. opinion, *supra* note 11, at 17–18.
45. *Design* and *Intend*, MerriamWebster (Online 2023), https://www.merriam-webster.com/dictionary.
46. *Coast Fed. Bank*, 323 F.3d at 1040.
47. U.S. Postal Inspection Serv., Prohibited, Restricted, and Non-Mailable Items (2022), https://bit.ly/3HCU4sY.
48. 18 U.S.C. § 1461.
49. O.L.C. opinion, *supra* note 11, at 2.
50. *Id.* at 14.
51. *Id.* at 14–15.
52. *Id.* at 12.
53. *Id.* at 15.
54. *Id.* at 12–13. This note also appears following the text of § 1461 in the U.S. Code. See *18 U.S. Code § 1461: Mailing Obscene or Crime-Inciting Matter*, Cornell L. Sch., https://www.law.cornell.edu/uscode/text/18/1461.
55. *Id.* at 12 n.14.
56. *Id.* at 11.
57. *Id.* at 14.
58. 576 U.S. 519 (2015).
59. *See* 42 U.S.C. § 3604.
60. *Id.* at 536.
61. *Id.* at 520.
62. *Id.* at 535.
63. *Id.* at 536.
64. *Id.*
65. *Id.*
66. With the exception of *Bours*, in fact, none of the appeals court decisions cited in the OLC opinion interpreted or applied the Comstock Act with regard to abortion.
67. Russello v. United States, 464 U.S. 16, 23 (1983), quoting United States v. Wong Kim Bo, 472 F.2d 720, 722 (5th Cir. 1972). *See also* Riegel v. Medtronic, Inc., 522 U.S. 312, 327 (2008) (When assessing two different clauses in the same statute to discern whether the Food, Drug, and Cosmetic Act's wording was intended to pre-empt state law for both drugs and medical devices, the court wrote: "It did not…but instead wrote a pre-emption clause that applies only to medical devices.")
68. *See* Sullivan v. Stroop, 496 U.S. 478 (1990).
69. 19 U.S.C. § 1905(a) (emphasis added).
70. O.L.C. opinion, *supra* note 11, at 8 n.9.
71. *See, e.g.*, U.S. v. One Package, 86 F.2d 737, 738 (2d Cir. 1936). The court's decision was based on a series of speculative phrases such as "seems hard to suppose," *id.* at 739, and "seems unreasonable." *Id.* at 740.
72. 62 Stat. 768.
73. 381 U.S. 479 (1965).
74. See Pub. L. 91–662, 62 Stat. 768 (1971).
75. Report of the Subcommittee on Criminal Justice on Recodification of Federal Criminal Law, 95th Cong., 39–42 (Comm. Print 1978) (emphasis added).

76. *Id.* at 39–42 (emphasis added).
77. H.R. 3057, 104th Cong. (1996).
78. In her remarks on the House floor, Schroeder focused on the Act's effect on abortion and criminalizing distribution of abortion information. She never said anything about "unlawful" or "illegal" abortion, but identified a violation of the statute as the strict liability offense it was. Schroeder said: "The problem is, this body just allowed the Comstock Act to be enforced on the Internet vis-à-vis anything doing with abortion. Previously, the Congress did away the Comstock Act dealing with family planning, thank goodness. But the Comstock Act has never been repealed; it is still on the books. And so, as a consequence, this has been thrown up on the Internet and could be used to bring people into a criminal conviction or arraignment if they decided to discuss anything about the big A word on the Internet.... The Telecommunications Act passed this year extended the Comstock Act's prohibitions to anyone who uses an interactive computer service. This Congress, therefore, revived Comstockery by making it a crime to use the Internet to provide or receive information which directly or indirectly tells where, how, of whom, or by what means an abortion may be obtained." Archives of Women's Political Communication, Iowa State University, posted March 21, 2017, https://awpc.cattcenter.iastate.edu/2017/03/21/comstock-act-still-on-the-books-sept-24-1996/.
79. Bours v. United States, 229 F. 960 (7th Cir., 1915).
80. *Id.* at 964.
81. *See supra* note 36.
82. *See* Comstock Law of (1873), *supra* note 5.
83. Information about Mifepristone for Medical Termination of Pregnancy Though Ten Weeks Gestation, U.S. Food and Drug. Admin. (2023), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-about-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation. *See also Mifepristone (Oral Route)*, Mayo Clinic, https://www.mayoclinic.org/drugs-supplements/mifepristone-oral-route/proper-use/drg-20067123#:~:text=For%20oral%20dosage%20form%20(tablets,dose%20placed%20in%20the%20cheeks; *Uses*, WebMD, https://www.webmd.com/drugs/2/drug-20222-325/mifepristone-oral/mifepristone-oral/details ("Mifepristone (also known as RU 486) is used to cause an abortion during the early part of a pregnancy.").
84. O.L.C. opinion, *supra* note 11, at 1.
85. *How Do I Use the Abortion Pill?*, Planned Parenthood, https://www.plannedparenthood.org/learn/abortion/the-abortion-pill/how-do-i-use-abortion-pill.

Article

The Linacre Quarterly
1-17

DOI: 10.1177/00243639221128389
journals.sagepub.com/home/lqr
SAGE

# Self-Managed Medication Abortion: Implications for Clinical Practice

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**Abstract**

Medication abortion represents more than 50 percent of abortions in the United States (US). Since its approval in the US in 2000, the Food and Drug Administration (FDA) has progressively relaxed the prescribing requirements such that currently, no office visit, in-person dispensing, or ultrasound is required. Obtaining medication for abortion online without medical supervision or evaluation is also possible. This article reviews the complications of medication abortion by examining major studies and delineates the risks specific to self-managed abortion to inform clinicians in caring for women.

**Summary:** Medication abortion has become the most common abortion method in the United States. This document provides a detailed history of the relaxation requirements on medication abortion and reviews the major studies on medication abortion complications including a discussion of their limitations. Finally, the paper delineates the ease of access to medication abortion without a health care provider and the risks associated with self-managed abortion. This paper is intended to provide information for clinicians who likely will be encountering increasing number of patients with such complications.

**Keywords**

Abortion, Abortion complications, Gynecology, Obstetrical care, Roe v. Wade, Women's reproductive health, Women's reproductive issues, Medication Abortion, Chemical Abortion, Mifepristone, Misoprostol

## Introduction

Medication abortion, approved in the United States (US) in 2000, now represents more than 50 percent of abortions in the US (Guttmacher Institute 2022a). It is accomplished with two medications: oral mifepristone, an anti-progesterone and buccal misoprostol, a uterotonic one to two days later. Bleeding usually lasts nine to sixteen days, and 8 percent of women bleed longer than thirty days ("Mifeprex Prescribing Information Revised 3/2016" 2016). The most common adverse events (AEs) are retained tissue and hemorrhage without transfusion, both of which can require surgical intervention. Other AEs include infection, hemorrhage requiring transfusion, ongoing pregnancy, and ectopic pregnancy.

Mifepristone is regulated under the Risk Evaluation and Mitigation Strategies (REMS), a drug safety program that the Food and Drug

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Administration (FDA) requires for certain medications with serious safety concerns to help ensure that the benefits outweigh the risks (Food and Drug Administration 2021b). The initial REMS required that the prescriber had to be a physician, the patient had to have three office visits, the medications had to be dispensed in certain health care facilities, and the physician had to be able to provide surgical intervention if needed, as well as ensure access to a hospital for resuscitation and transfusion if necessary (Food and Drug Administration 2011; US Government Accountability Office 2018; Center for Drug Evaluation and Research 2016). The physician was also required to report all serious AEs. These measures are no longer required; in many states, abortion can be obtained legally via telemedicine (Guttmacher Institute 2022b).

With the overturn of Roe v. Wade on June 24, 2022 (Supreme Court of the United States 2022), some states are enacting bans or restrictions on abortion, and women may increasingly turn to self-managed abortion with pills obtained online. The objective of this article is to review the complications of medication abortion by examination of significant studies and to delineate the risks specific to self-managed abortion to inform clinicians in caring for women who present with complications.

## Pharmacology of Mifepristone

Mifepristone is a selective progesterone receptor modulator that binds to the progesterone receptor in the uterus with a higher affinity than progesterone but does not activate the receptor, thus acting as an anti-progesterone (ACOG 2020). It directly blocks the progesterone production by the corpus luteum and also blocks the decidual response to progesterone, resulting in fetal death. Other actions of mifepristone on the pregnant uterus include cervical softening, increased uterine contractility, and sensitivity to prostaglandins (ACOG 2020). Mifepristone interferes with the ability of the spiral arteries to contract, which is the primary method of hemostasis after the placenta separates from the decidua. At higher doses, mifepristone has anti-glucocorticoid activity (Autry and Wadhwa 2022). It blocks cortisol receptors in central and peripheral tissues. The drug was initially developed to treat Cushing's disease (Department of Health and Human Services et al. 2006).

Mifepristone use in medication abortion has been associated with infection, specifically *Clostridium sordellii (C. sordellii).* Nine of the twenty-four US deaths after medication abortion (as of 2018) were from sepsis, five of which were from *C. sordellii* (Aultman et al. 2021). Four women died in California after medication abortion from 2003 to 2005 from *C. sordellii* sepsis. In response, the "Emerging Clostridial Diseases" workshop was held by the Department of Health and Human Services, the Center for Disease Control and Prevention, the FDA, and the National Institutes of Health (Department of Health and Human Services et al. 2006). This workshop discussed how mifepristone's anti-progesterone activity on the pregnant uterus predisposes it to infection. It was delineated that cervical ripening, decidual ischemia, and necrosis of the products of conception enable the decidua to become a favorable nidus for infection by the anaerobic bacteria, *C. sordellii* (Department of Health and Human Services et al. 2006, 107). It was also proposed that the anti-glucocorticoid activity of mifepristone impairs the functioning of the pregnant uterus' innate immune system, also predisposing to *C. sordellii* (Department of Health and Human Services et al. 2006, 107). These mechanisms are further delineated in peer-reviewed literature. (Aronoff et al. 2008; Miech 2005).

## Pharmacology of Misoprostol

Misoprostol is a prostaglandin E1 analog approved by the FDA for gastric ulcer prevention for those on long-term nonsteroidal anti-inflammatory drugs. Misoprostol inhibits gastric acid secretion and protects the mucosa. It also causes uterine contractions. Misoprostol is widely used in obstetrics for cervical ripening,

labor induction, and control of postpartum hemorrhage. Side effects of misoprostol include diarrhea, abdominal pain, nausea, flatulence, headache, dyspepsia, vomiting, and constipation (Pfizer 2021). Misoprostol is a known teratogen associated with Mobius sequence, terminal transverse limb defects, and other malformations. These malformations have been attributed to the common mechanism of fetal vascular disruption (Vauzelle et al. 2013).

## The FDA and Medication Abortion

Understanding the history of the FDA's decisions toward progressively fewer requirements on medication abortion is essential, as it has provided the path to less physician involvement and increasing ease of obtaining this REMS-restricted medication. Medication abortion with mifepristone and misoprostol was initially approved in the US in September 2000 under restricted distribution regulations (Center for Drug Evaluation and Research 2000). The dosing regimen was mifepristone 600 mg orally, followed two days later by misoprostol 400 mcg orally. It was approved for up to forty-nine days of gestation, and there were three required office visits (days one, three, and fourteen). The prescriber had to be a licensed physician who could accurately assess the duration of pregnancy, diagnose ectopic pregnancies, and provide surgical intervention if necessary (or have made plans to provide such care through other qualified physicians). The prescribing physician had to ensure patient access to medical facilities equipped to provide blood transfusion and resuscitation if necessary. The medications had to be dispensed in a clinic, medical office, or hospital. The physician was required to sign and return the prescriber agreement form. Additionally, the abortion provider had to report any hospitalization, transfusion, serious event, or ongoing pregnancy (US Government Accountability Office 2018, 7). In 2011, the FDA instituted REMS, which incorporated the 2000 requirements (FDA 2011).

In 2016, the prescribing requirements were modified significantly. The approval was extended to seventy days gestation, only one office visit was required (a follow-up visit on days seven to fourteen), and the prescriber no longer had to be a physician. The dose of mifepristone was decreased to 200 mg, misoprostol was increased to 800 mcg, and the misoprostol route was changed from oral to buccal. A repeat dose of misoprostol could be given if the pregnancy was not expelled. At the same time that the prescribing requirements were relaxed, the AE reporting requirements were eliminated except for the requirement to report death (US Government Accountability Office 2018, 8).

In July 2020, a federal judge suspended the requirement for in-person dispensing during COVID-19 (American College of Obstetricians and Gynecologists et al., v. Food and Drug Administration et al. 2020). This requirement was overturned by the US Supreme Court in January 2021 (Supreme Court of the US 2021). In April 2021, after the American College of Obstetricians and Gynecologists (ACOG) advocated for women to receive medication abortion without in-person assessment, the FDA replied that they would not enforce any in-person requirements (Woodcock 2021). The April 2021 letter from FDA to ACOG documented a low rate of reported AEs, ignoring that reporting of AEs (except death) was no longer required. The FDA also identified four publications with relevant clinical outcomes and concluded that, although there were limitations in study designs, the findings did not appear to show an increase in serious safety concerns with modification of the in-person requirement. In December 2021, the FDA removed the requirement to dispense medication abortion pills in a healthcare setting, allowing for mail-order medication abortion (FDA 2021a). Table 1 summarizes the progression of relaxed restrictions on medication abortion. States may have further restrictions, but the FDA does not require an office visit, ultrasound, or physician. Although the prescriber must be able to assess pregnancy duration and diagnose ectopic pregnancy accurately, no visit or ultrasound is required.

**Table 1.** Changes in FDA Requirements for Medication Abortion.

| | 2000 | 2016 | 2020 | 2021 |
|---|---|---|---|---|
| Gestational Age (GA) | 49 days | 70 days | 70 days | 70 days |
| Number of Office Visits | 3 | 1 | 0 | 0 |
| Prescriber | Physician | Healthcare Provider | Healthcare Provider | Healthcare Provider |
| Dispensing Location | Health care facility | Health care facility | Health care facility | Certified Pharmacy |
| Reporting Requirements | All serious events | Death | Death | Death |

The FDA Adverse Event Reporting System (FAERS) is a mechanism for reporting adverse medication events. Anyone can submit an Adverse Event Report (AER) to the FDA for a medication. The database is available online ("FDA Adverse Event Reporting System"). When medication abortion was first approved, the prescriber was required to report any hospitalization, transfusion, serious AE, or ongoing pregnancy (Center for Drug Evaluation and Research 2000; FDA 2011). When the REMS were relaxed in 2016, the prescriber was no longer required to report AEs except death (US Government Accountability Office 2018, 8).

Although the FAERS is a database of AEs, it is not a comprehensive list of all AEs. Even when reporting was required, the only obligate reporter was the prescriber. Complications are often treated by someone other than the abortion provider. Aultman et al. was a study of the AERs submitted to the FDA for medication abortion, and in that study, less than 40 percent of the D&Cs for complications were performed by the abortion provider (Aultman et al. 2021).

One study demonstrated that even when reporting was required, not all AEs known to the abortion provider appeared in FAERS (Cirucci, Aultman and Harrison 2021). Cleland et al. published a study of medication abortion complications in 2013 and based their data on the AERs that Planned Parenthood reported to the manufacturer, Danco Laboratories (Danco) who then submitted them to the FDA. Cleland stated, "In accordance with the mifepristone prescribing information, Planned Parenthood Federation of America reports all significant adverse events and outcomes to Danco Laboratories, the US distributor of mifepristone, which in turn reports them to the FDA" (Cleland et al. 2013). Cirucci et al. reported discrepancies between the AEs that Planned Parenthood reported in 2009 and 2010 (according to Cleland et al.) and those on the FAERS online dashboard. According to Cleland et al., Planned Parenthood reported 1530 AERs/cases to Danco for 2009 and 2010, yet only 664 AERs are listed on the FAERS dashboard for that period. The FAERS should have more AERs than Planned Parenthood reported since Planned Parenthood performs only 37 percent of US abortions (Abortion Care Network 2020). This discrepancy demonstrates that even the known AEs that were supposedly reported do not all show up in the FAERS. Cirucci et al. conclude, "These discrepancies, and the fact that since 2016, reporting AEs other than deaths is no longer required, demonstrate that the FAERS is inadequate to evaluate the safety of mifepristone" (Cirucci, Aultman and Harrison 2021).

According to the FDA, from September 2000 to December 2018, out of 3.7 million medication abortions in the US, there were only 4,195 with any AE, including non-severe AEs (Food and Drug Administration 2018), a 0.11 percent complication rate. Even a conservative 2 percent complication rate would

generate 74,000 AEs, raising concern that less than 6 percent of actual AEs are included in the FAERS.

## Complications of Medication Abortion

As physicians, we often look not to government databases but to peer-reviewed studies. There are a plethora of studies evaluating medication abortion. Several significant studies will be examined here. Many assert the safety of medication abortion, and a detailed evaluation of these studies is helpful.

Chen et al. in 2015 did a systematic review of 20 studies (n = 33,846) and provided results that seemed to support the safety of medication abortion (Chen and Creinin 2015). Chen et al. reported an efficacy rate of 96.7 percent up to sixty-three days gestation (n = 33,514) and 93.1 percent from sixty-four to seventy days (n = 332). The ongoing pregnancy rate was 0.8 percent up to sixty-three days gestation and 2.9 percent from sixty-four to seventy days. Transfusions (0.03%–0.6%) and hospitalizations (0.04%–0.9%) were uncommon. Emergency room (ER) visits occurred in 2.9 percent to 3.7 percent of patients, and surgical evacuation (other than for ongoing pregnancy) occurred in 1.8 percent to 4.2 percent. In Chen's review, 76 percent of the data was from two retrospective studies. One of these (n = 13,373) did not evaluate ER visits (Gatter, Cleland and Nucatola 2015), and the other study (n = 11,155) did not evaluate ER visits or hospitalizations (Goldstone, Michelson and Williamson 2012). The loss to follow-up in these two studies was 15.5 percent and 16 percent, respectively.

Another systematic review, performed by Raymond et al. (Raymond et al. 2013), included 87 trials and 120 trial groups (n = 45,528). Raymond et al. reported efficacy of 95.2 percent, ongoing pregnancy of 1.1 percent, transfusion of 0.1 percent, and hospitalization of 0.3 percent (1.1% in the largest study). Only seven studies in this systematic review had more than 1,000 patients; the largest study had 4132 patients. The studies had various doses and routes of medication. Overall, 4.8 percent of women required surgical completion.

Ireland et al. performed a retrospective cohort study comparing medical abortion (n = 13,221) to surgical abortion (n = 16,925) (Ireland, Gatter and Chen 2015). For medical abortions, Ireland et al. reported an efficacy of 99.6 percent, based on the 0.4 percent ongoing pregnancy rate, but excluding the 2.2 percent of cases that required surgical aspiration. The reported rate of major complications was low (0.007%), as was persistent pain, bleeding, or both (1.8%). Ireland et al. reported the risk of any AEs as 2.2 percent. There was a 15.9 percent loss to follow-up rate, and those lost to follow-up were not excluded but were assumed to have had an uncomplicated complete abortion. Medication abortion had four times the risk of failure compared to surgical abortion and the ongoing pregnancy rate increased by 50 percent for each week of gestational age (GA).

Cleland et al. analyzed all Planned Parenthood medication abortions from 2009 to 2010 (n = 233,805) (Cleland et al. 2013). Eight specific AEs were evaluated and the study reported low rates of complications: ER treatment (0.10%), hospital admission (0.06%), transfusion (0.05%), intravenous (IV) antibiotics (0.02%), infection requiring IV antibiotics or admission (0.016%), ongoing pregnancy (0.50%), ectopic pregnancy (0.007%), and death (one death: 0.0004%). Cleland et al. reported an overall complication rate of 0.65 percent but did not evaluate retained products of conception, hemorrhage without transfusion, or incomplete abortion if treated at the clinic. Cleland et al. state that the data are only those reported to or received by Planned Parenthood and did not provide the percentage of patients lost to follow-up.

International studies show a different picture of the frequency of complications. Carlsson et al. reported on all induced abortions at Skaraborg Hospital, Sweden from 2008 to 2015 (n = 4945) (Carlsson, Breding

and Larsson 2018). Of these, 74.7 percent were medication abortions before twelve weeks. All patients had a pre-abortion evaluation consisting of a visit with a gynecologist at the clinic, a pelvic exam, vaginal ultrasound, and screening for infection. For medical abortion under twelve weeks, the rate of incomplete abortion was 4.1 percent, and the overall complication rate was 7.3 percent. Interestingly, the complication rate doubled from 4.2 percent to 8.2 percent during the study period.

Niinimaki et al. evaluated all abortions in Finland from 2000 to 2006 (n = 42,619) to estimate the immediate AEs and safety of medical versus surgical abortion (Niinimaki et al. 2009). Using high-quality data from the National Health Registry, this study included all abortions in Finland for up to sixty-three days and followed them for six weeks post-abortion. Niinimaki et al. found that hemorrhage occurred in 15.6 percent of those who had medication abortion compared to 2.1 percent of those who had a surgical abortion. Niinimaki et al. did not define hemorrhage but included all reported hemorrhages. The Society of Family Planning notes that hemorrhage after abortion has been variably defined (with definitions including more than 250 ml blood loss, more than 500 ml blood loss, requiring hospitalization, and requiring transfusion) and suggests that a clinically relevant definition would include both a clinical response and/or bleeding greater than 500 ml (Kerns and Steinauer 2013). Niinimaki et al. note that since medical abortion is associated with bleeding lasting approximately two weeks, the high rate of consultation for bleeding is not surprising. They suggest that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after pregnancy termination. Niinimaki et al. found that surgical re-evacuation was required in 5.9 percent and 1.8 percent for medication and surgical abortion, respectively. Incomplete abortion occurred in 6.7 percent of those who had a medication abortion compared to 1.6 percent of those who had a surgical abortion. The risk of infection was 1.7 percent for both. The study found that 20 percent of women who had a medication abortion suffered a complication compared to 5.6 percent of those who had a surgical abortion, almost four times the risk of complications.

Other studies confirm that medication abortion has higher complication rates than surgical abortion. Upadhyay et al. showed that first-trimester medication abortion had nearly six times the risk of complications compared to surgical aspiration (Upadhyay et al. 2015). In Ireland et al., medication abortion had four times the risk of failure compared to surgical abortion (Ireland, Gatter and Chen 2015). Studnicki et al. showed that medication abortion is more than twice as likely to result in an abortion-related ER visit (Studnicki et al. 2021).

A register-based cohort study by Mentula et al. demonstrated that risks of medication abortion increase with increasing GA (Mentula et al. 2011). The study evaluated 18,248 cases of medication abortion in Finland between 2003 and 2006. A surgical evacuation was required in 7.9 percent of first-trimester abortions compared to 38.5 percent of second-trimester abortions. Infection occurred in 1.9 percent of those who underwent a medication abortion in the first trimester compared to 4.0 percent in the second trimester.

### *Telemedicine Abortion*

Telemedicine is the delivery of healthcare services by healthcare professionals utilizing telecommunications technology (Endler et al. 2019; Galle et al. 2021). One of the advantages of telemedicine is increased access; patients who live remotely or cannot obtain transportation can access care from home, which is particularly important in underserved populations. The increased access must be balanced with privacy issues and the lack of a physical exam and in-person face-to-face interaction. Although an evaluation of the literature on telemedicine, in general, is beyond the scope of this article, some significant studies on telemedicine abortion will be presented.

Endler et al. performed a systematic review of telemedicine abortion, which consisted of

31,223 medication abortions (Endler et al. 2019). For pregnancies of ten weeks or less GA, ongoing pregnancy rates ranged from 0 percent to 1.9 percent (1.3% to 2.3% over ten weeks). Complete abortion (self-assessed) was reported in 93.8% to 96.4%, and surgical evacuation was required in 0.9 percent to 19.3 percent (8.5% to 20.9% over ten weeks). Blood transfusion occurred in 0% to 0.7% and hospitalization occurred in 0.07 percent to 2.8 percent. In this systematic review, most studies were descriptive, and there were no randomized controlled trials. Most outcomes were self-reported, and all study groups were high-to-middle income and therefore not necessarily applicable to all socioeconomic groups. Endler et al. concluded that "success rate and safety outcomes are similar to those reported in the literature for in-person abortion care, and surgical evacuation rates are higher." However, they admitted that due to high heterogeneity, the evidence must be interpreted with caution (Endler et al. 2019). The loss to follow-up was 5 percent to 57 percent, and the authors rated the evidence's quality as low.

Grossman et al. documented a retrospective cohort study in Iowa and compared all medication abortions performed by telemedicine or in-person at a clinic system in Iowa from July 1, 2008 to July 30, 2015 (Grossman and Grindlay 2017). The telemedicine patients were evaluated by clinic staff, including a focused physical exam, hemoglobin, and ultrasound, and they later met with a physician off-site via video. The study evaluated hospital admissions, surgery (not including vacuum aspiration), blood transfusion, ER treatment, and death. The data was obtained from the AERs that Planned Parenthood submitted to Danco, any self-reported events, and a low-response rate ER survey. Grossman et al. reported 49 clinically significant AEs out of 19,170 medical abortions. The complication rate for telemedicine abortions (n = 8765) was 0.18 percent and that for in-person abortions (n = 10,405) was 0.32 percent. Some significant AEs were excluded from the study, including incomplete abortions if treated at a clinic, ongoing pregnancies, nonserious events treated as an outpatient, and ectopic pregnancies captured by another category. A lower complication rate for telemedicine abortion than in-person does not seem plausible. The data was based on the AERs submitted to the FDA, required for only certain complications at the time of the study. Importantly, all patients in the telemedicine group had an exam and ultrasound, not necessarily replicating other telemedicine protocols.

Raymond et al. reported on the Gynuity TelAbortion study (Raymond et al. 2019; Gynuity). Each patient had a videoconference with a healthcare provider, lab testing, and an ultrasound before an abortion. Pills were sent via mail, and the patients had a follow-up visit with a healthcare provider by phone or video. There were 433 screenings, of which 268 had a telemedicine evaluation, and 248 were sent packages of pills. There were fifty eight (23.4%) with unknown outcomes and two patients who chose not to take the pills. Of the remaining 188 with known outcomes, 6 percent required surgical completion. Despite a known outcome in only 190 patients, the authors claimed a "meaningful follow-up" in 217 patients. Of these, two (1%) had a serious AE (one a seizure after aspiration and one a hemoglobin of 6.3 g/dl requiring transfusion). The authors "judged that neither event would have been averted had the abortion medications been provided in person" (Raymond et al. 2019). Sixteen (7%) other patients went to the ER. Of those who were Rh-negative, 31 percent did not receive Rh D Immune globulin. The authors concluded, "This direct-to-patient telemedicine abortion service was safe, effective, efficient, and satisfactory" (Raymond et al. 2019). Again, the pre-abortion testing, including ultrasound, does not necessarily replicate other telemedicine abortion protocols.

There is a range of protocols for telemedicine abortion. In both Raymond's and Grossman's studies, all women had an ultrasound. A woman who gets blood work and an ultrasound locally and then meets with a physician via video has more safety measures

than a woman who only has a video visit without additional evaluation. These issues are particularly pertinent with the push toward medication abortion without ultrasound to determine pregnancy location or GA (Schmidt-Hansen 2020; Goldberg et al. 2022). The FDA requires the provider to be able to assess the duration of pregnancy and diagnose ectopic pregnancy yet requires no in-person visit (Woodcock 2021; FDA 2021a).

## Self-Managed Abortion

Another way women can access abortion is by ordering pills online without medical supervision. In this article, telemedicine abortion has been used to refer to abortion pills obtained with remote interaction with a healthcare provider, either by video or phone. The term "self-managed abortion" will be used in this article to refer to obtaining abortion pills online, by mail, or by other means without any oversight by a health care provider and is distinguished from telemedicine abortion.

### *How to Obtain Abortion Pills for Self-Managed Abortion*

Obtaining abortion pills online is easy and accessible even in states where telemedicine is restricted. "Plan C" has a website that says, "A safe, at-home abortion is here," and guides the person through the process, with different options tailored for each state ("A Safe at-home abortion is here"). The site provides four categories to obtain abortion pills: (1) telehealth, (2) online pharmacies, (3) mail forwarding for states in which telehealth is restricted, and (4) in-person. The first of these options, telehealth, sends the person to Aid Access (and sometimes other options depending on the state), a website that provides an online consult for abortion pills by mail. Dutch physician Rebecca Gomperts founded Aid Access (Aid Access). After determining that Aid Access caused the introduction into interstate commerce of misbranded and unapproved drugs, the FDA in 2019 requested Gomperts to "immediately cease causing the introduction of these violative drugs into US commerce" (FDA 2019). Gomperts' lawyer responded, "When US women seeking to terminate their pregnancies consult Dr. Gomperts, she will not turn them away" (Hearn Law PLC 2019). On her website, Gomperts wrote that she would not be deterred and would continue to provide abortion services (Gomperts 2019). Aid Access continues to provide abortion pills by mail.

Aiken et al. published a retrospective evaluation of the safety and effectiveness of self-managed abortion obtained via Aid Access (Aiken et al. 2022). The dataset (n = 4,583) included all the US residents who were sent abortion medications between March 20, 2018 and March 20, 2019. Four weeks after receipt of the medications, users were invited to report their abortion outcomes using an online evaluation tool or via email. Among 4,583 who received abortion pills, 3,186 (69.5%) provided follow-up information. Of these, 2,797 (88%) took the medication. Of those who took the medication, 96.4% terminated their pregnancy without surgical intervention, 1.0 percent reported treatment for any serious AE, 0.6 percent reported receiving a blood transfusion, and 0.5 percent reported receiving IV antibiotics. The authors reported that one of the study's limitations is that outcomes were self-reported and noted that the follow-up rate was 70 percent. They note that this follow-up rate is "on par with or better than many clinical studies since most outcomes are only recorded if patients decide to follow up with the clinic" (Aiken et al. 2022).

The second option in Plan C, online pharmacies, provides a list of five online pharmacies and the cost and lead time to get pills. "Shoppers" can put the pills in their shopping cart on these sites, similar to purchasing a book on Amazon. Option three provides several "creative ways" to access pills in states where telehealth is restricted, including mail forwarding, picking up in neighboring states, and general delivery in a neighboring state. Regarding mail forwarding for women in Texas, the website states, "You live in a state that restricts access to abortion, but alternate routes of access may still be possible.

People in your state are getting abortion pills by mail and having medically-safe abortions at home by using: Aid Access, Online pharmacies, Mail forwarding, Pickup in Mexico" ("The Plan C Guide to Abortion Pills: How to get abortion pill access by mail in Texas"). The fourth option provides a list of in-person clinics and abortion providers. The pills for medication abortion are accessible to anyone who may want to obtain them.

### *Complications With Self-Managed Abortion*

In addition to the previously discussed risks of medication abortion, providers should be aware of additional concerns with women obtaining pills online without medical consultation. The issues of estimated GA, ectopic pregnancy, Rh incompatibility, access to care for complications, informed consent, and forced abortion are issues that must be forefront as self-managed medication abortion increases.

### *Estimation of GA*

In self-managed medication abortion, the GA is typically determined by a woman's self-reported date of last menstrual period (LMP) (Aid Access). Accurate determination of GA is essential because risks of medication abortion increase with increasing GA (Mentula et al. 2011; Bartlett et al. 2004). In Mentula et al., surgical evacuation was required in 7.9% of first trimester abortions and 38.5% of second trimester abortions. Infection occurred in 1.9% of first trimester abortions and 4.0% of second trimester abortions (Mentula et al. 2011). Bartlett et al. evaluated risk factors for induced abortion-related mortality in the US and found that, "Women whose abortions were performed in the second trimester (at or after 13 weeks of gestation) had abortion-related mortality rates greater than women whose abortions were performed in the first 8 weeks of pregnancy (RR at 13–15 weeks, 14.7 [95% CI 6.2, 34.7]; RR at 16–20 weeks, 29.5 [95% CI 12.9, 67.4]; RR at or after 21 weeks, 76.6 [95% CI 32.5, 180.8]). If women who had abortions after 8 weeks of gestation had obtained abortions during the first 8 weeks of pregnancy, when risk is lowest, 87% of deaths likely could have been prevented." (Bartlett et al. 2004). Currently, medication abortion is approved up to seventy days gestation. In the first trimester, ultrasound is the most accurate method to determine GA (ACOG 2017a). In one study, 40 percent of women had their due date adjusted because of a discrepancy of more than five days in dating by ultrasound compared to dating by LMP (Bennett et al. 2004). Without an ultrasound to determine GA, medication abortion might inadvertently occur beyond the seventy-day limit, with subsequent potential for significant complications. Although ACOG states that an ultrasound is the most accurate method to determine GA, their Practice Bulletin on medication abortion states that no ultrasound or clinical examination is required for women with regular menstrual cycles, a certain LMP within the past fifty-six days, and no signs, symptoms, or risk factors for ectopic pregnancy (ACOG 2020). In a study in India on the safety of providing abortion pills without a prescription, 27.5 percent of women who presented to the hospital had consumed abortion pills beyond the approved GA of nine weeks, and 17.5 percent had consumed the pills after twelve weeks (Nivedita and Shanthini 2015).

### *Ectopic Pregnancy*

Ectopic pregnancies represent 2 percent of all reported pregnancies and 2.7 percent of pregnancy-reported deaths. Half of the women with ectopic pregnancies do not have risk factors (ACOG 2018). Ectopic pregnancy is a contraindication for medication abortion. Administration of medication for abortion without confirmation of pregnancy location has ended in undiagnosed and ruptured ectopic pregnancies (Aultman et al. 2021; Wang et al. 2021). Two of the 24 deaths from medication abortion in the US since 2000 resulted from ruptured ectopic pregnancies (Food and Drug Administration 2018).

Without an ultrasound to determine pregnancy location before administering mifepristone and misoprostol, ectopic pregnancies may be missed. Further, symptoms of ectopic pregnancy such as bleeding and pain can be easily attributed to the abortion process. Medication abortion without ultrasound is increasingly promoted (Schmidt-Hansen et al. 2020; Goldberg et al. 2022). Administering medications for abortion without confirmation of pregnancy location and GA is inconsistent with good medical practice, and bad outcomes have resulted (Gary and Harrison 2006; Food and Drug Administration 2018; Wang et al. 2021; Aultman et al. 2021). In the two papers categorizing the FDA AERs up to February 2019, there were a total of ninety-two ectopic pregnancies (Gary and Harrison 2006; Aultman et al. 2021). Gary and Harrison detail seventeen ectopic pregnancies, eleven of which were ruptured, one of which resulted in death (Gary and Harrison 2006). Aultman et al. detail seventy-five ectopic pregnancies, at least twenty six of which were ruptured (twenty-five rupture status is not given), one of which resulted in death (Aultman et al. 2021). If a woman attempting a self-managed abortion has an ectopic pregnancy, the lack of physician involvement can be catastrophic.

### *Rh Incompatibility*

In North America, approximately 15 percent of women are Rh-negative (ACOG 2017b). ACOG states, "Rh D immune globulin should be given to Rh D-negative women who have pregnancy termination, either medical or surgical" (ACOG 2017b). In another ACOG bulletin, ACOG states that Rh testing is recommended before medication abortion, but if testing and Rh D immunoglobulin are unavailable or would significantly delay the abortion, shared decision-making is recommended (ACOG 2020). In untreated iso-immunized infants, 14 percent are stillborn, and half suffer neonatal death or brain injury (Zipursky and Paul 2011). Rh D immune globulin has decreased isoimmunization from 13 to 16 percent to 0.5 to 1.8 percent in a subsequent pregnancy (ACOG 2017b). As noted previously, in one telemedicine abortion study, 31 percent of Rh-negative women did not receive Rh D Immune globulin. For self-managed abortion, it is unclear how Rh-negative women will receive Rh D Immune globulin

### *Access to Medical Care for Complications*

The FDA mandates that the prescriber be able to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others and also must assure patient access to medical facilities equipped to provide blood transfusions and resuscitation if necessary (Center for Drug Evaluation and Research 2016; Danco Laboratories 2016). If a woman obtains an abortion by pills online, it is unclear who will care for any complications and what will be her recourse if she does not have close access to an ER. It is essential that women who undergo medication abortion, whether self-managed or not, have access to emergency care.

### *Informed Consent*

Physicians are responsible for providing informed consent for any medical treatment or intervention. Patients have the right to understand the risks, benefits, pros, and cons. The National Academies of Science 2018 Report on The Safety and Quality of Abortion Care in the US says, "Thus, when women seek an abortion, they should have the opportunity to discuss their questions and concerns and receive support in their decision making" (National Academies of Science, Engineering, & Medicine 2018, 46). ACOG states that "Meeting the ethical obligations of informed consent requires that an obstetrician–gynecologist gives the patient adequate, accurate, and understandable information and requires that the patient has the ability to understand and reason through this information and is free to ask questions and to make an intentional and voluntary choice, which

may include refusal of care or treatment" (ACOG 2021). ACOG also recommends shared decision-making which is a "patient-centered, individualized approach to the informed consent process that involves discussion of the benefits and risks of available treatment options in the context of a patient's values and priorities." Unlike telemedicine, where a physician and patient can discuss the risks and benefits of a given intervention, there is no such interaction when pills are obtained online.

### *Forced Abortion*

One concern with online abortion is that the medication may be obtained by someone other than the patient. The covert use of abortion pills in a woman's food or drink has been documented even before the relaxation of restrictions. In 2007 in Wisconsin, Manishkumar Patel spiked his girlfriend's smoothie with mifepristone and was sentenced to twenty-two years in prison ("Wisconsin man spikes mistress's drink with abortion drug, gets 22 years in prison" 2018). In 2014, Scott Bollig in Kansas purchased pills on the internet and put them in his girlfriend's pancake, resulting in the unborn child's death ("Man accused of killing fetus with 'abortion pancake'" 2014). In 2017, Dr. Sikander Imran in Virginia put mifepristone in his girlfriend's tea, resulting in the death of the fetus. He pled guilty to fetal homicide ("Doctor sentenced for spiking girlfriend's drink to induce abortion" 2018; McBride 2017). In 2018, Jeffrey Smith in Wisconsin tried to kill his unborn child by putting mifepristone in his girlfriend's water bottle and was later convicted of attempted first-degree intentional homicide of an unborn child and sentenced to twenty years in prison (Siewert 2022). When these situations occurred, mifepristone was required to be dispensed in specific healthcare settings (clinics, medical offices, hospitals) under the supervision of a certified prescriber (FDA 2011, 2; Center for Drug Evaluation and Research, 2016, 3). Dispensing in a healthcare setting is no longer required (FDA 2021a), even for legal medication abortion.

Forced abortion is common among trafficked women. In Lederer's survey of 2014 human trafficking survivors, 55.2 percent of them had at least one abortion, 29.7 percent had multiple abortions, and 52.9 percent had one or more abortions partly or wholly forced on them (Lederer and Wetzel 2014). One victim reported that "in most of [my six abortions,] I was under serious pressure from my pimps to abort the babies" (Lederer and Wetzel 2014). Another trafficking victim reported seventeen abortions and indicated that at least some were forced on her. With the ability to obtain abortion pills online, traffickers can more easily accomplish forced abortions on their victims. Healthcare providers are one of the few professionals with whom trafficked women and girls are likely to interact and are uniquely positioned to identify and provide care for these victims (Dovydaitis 2010). As self-managed abortion becomes accessible, we must be aware of the increased possibility of forced abortions and look for ways to protect women.

## Clinical and Ethical Implications

We are in an unprecedented time in the US. With the recent overturn of Roe v. Wade, some states seek to become abortion sanctuaries and are increasing access; other states are enacting abortion bans and restrictions. We can expect that women will increasingly access abortion pills online in states where abortion is restricted. These women may present to our offices and ERs, and it is essential to be aware of the medical implications as well as the personal situations that factor into their decisions.

Our ethical responsibility is to be vigilant of these complications and to care for women. We must continue to provide services to provide a safety net and to care for those with at-risk pregnancies. Black women are particularly at risk since the abortion rate is highest in black women (21.2 abortions per 1,000 women) than in White (6.3 per 1,000), Hispanic (10.9 per 1,000), or other races (11.9 per 1,000) (Kortsmit et al. 2021).

According to the latest CDC Abortion Surveillance Report, 38.4 percent of reported abortions were in Black women (Kortsmit et al. 2021), yet the population percentage is only 13.6 percent (US Census Bureau 2021).

In an ideal world, no one would get an abortion. However, we do not live in an ideal world, and women will continue to obtain abortions. It is essential to be aware of the complications germane to self-managed abortion so that we can provide the best care.

## Conclusion

Any medical intervention or procedure has risks. It is our responsibility as physicians to advise our patients of risks and discuss options. We must work to minimize the risks and promote the best outcome. Finally, when we care for pregnant women, we have two patients: the mother and her baby. When a woman chooses to end her baby's life, our responsibility remains to care for the woman. Currently, in the US, the FDA has reduced safety measures even where abortion is legal. In places where it is not, women will continue to access pills online and through creative means. Both of these scenarios raise concerns about increasing harm to women. Access and availability must never supersede safety and care for women. Nevertheless, we will continue to care and advocate for our patients and manage their complications when they occur.

### Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author received no financial support for the research, authorship, and/or publication of this article

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*Systematic Review*

**SAGE Open Medicine**

SAGE Open Medicine
Volume 5: 1–17

DOI: 10.1177/2050312117740490
journals.sagepub.com/home/smo
SAGE

# Pregnancy associated death in record linkage studies relative to delivery, termination of pregnancy, and natural losses: A systematic review with a narrative synthesis and meta-analysis

**David C Reardon[1] and John M Thorp[2]**

## Abstract

**Objectives:** Measures of pregnancy associated deaths provide important guidance for public health initiatives. Record linkage studies have significantly improved identification of deaths associated with childbirth but relatively few have also examined deaths associated with pregnancy loss even though higher rates of maternal death have been associated with the latter. Following PRISMA guidelines we undertook a systematic review of record linkage studies examining the relative mortality risks associated with pregnancy loss to develop a narrative synthesis, a meta-analysis, and to identify research opportunities.
**Methods:** MEDLINE and SCOPUS were searched in July 2015 using combinations of: mortality, maternal death, record linkage, linked records, pregnancy associated mortality, and pregnancy associated death to identify papers using linkage of death certificates to independent records identifying pregnancy outcomes. Additional studies were identified by examining all citations for relevant studies.
**Results:** Of 989 studies, 11 studies from three countries reported mortality rates associated with termination of pregnancy, miscarriage or failed pregnancy. Within a year of their pregnancy outcomes, women experiencing a pregnancy loss are over twice as likely to die compared to women giving birth. The heightened risk is apparent within 180 days and remains elevated for many years. There is a dose effect, with exposure to each pregnancy loss associated with increasing risk of death. Higher rates of death from suicide, accidents, homicide and some natural causes, such as circulatory diseases, may be from elevated stress and risk taking behaviors.
**Conclusions:** Both miscarriage and termination of pregnancy are markers for reduced life expectancy. This association should inform research and new public health initiatives including screening and interventions for patients exhibiting known risk factors.

## Keywords

Maternal mortality, pregnancy associated death, longevity, pregnancy loss, termination of pregnancy, abortion, miscarriage, risk factors, pregnancy screening, health policy

Date received: 9 November 2016; accepted: 9 October 2017

## Introduction

Maternal deaths associated with pregnancy are a major public health concern. Death rate calculations based on death certificates alone, however, consistently miss cases due to the fact that registrars often lack information about the deceased's woman's complete pregnancy history. This problem can be alleviated in part by linking death certificates to birth certificates, fetal death records, termination of pregnancy (TOP) registries, and medical treatment records.

Without such record linkage only 26% of deaths during pregnancy or after live birth or stillbirth would have been

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identified from the death registry or death certificates alone, according to a Finnish study.[1] Using death certificates alone, only 12% of deaths following miscarriage or ectopic pregnancy and just 1% of deaths following termination of pregnancy (TOP) could be identified without record linkage.[1] The importance of systematically using record linkage to identify deaths associated with pregnancy losses (TOP, miscarriage, and ectopic pregnancies) is further demonstrated by the same study's findings, which demonstrate that the mortality rate in the year following a pregnancy loss was two to four times higher than that of delivering women.

Record linkage studies are therefore clearly necessary to properly identify the effects of pregnancy on the health and longevity of women. This methodology is especially important to understanding mortality rates associated with TOP and natural pregnancy losses precisely because such deaths are (a) much more common than deaths during pregnancy or after delivery, and (b) less likely to be identified on death certificates alone.[1]

Compared to women who deliver, those who miscarry or have TOP face significantly elevated rates of psychiatric disorders,[2–10] substance use,[5,6,10–13] suicidal behaviors,[5,6,13–16] sleep disorders,[17] post-traumatic stress disorders,[7,18,19] a decline in general health,[20] and elevated rates of recourse to medical treatments in general,[21,22] most of which have been observed within the first through ten years following the pregnancy loss. Any and all of the aforementioned conditions may shorten longevity. It is therefore especially important from a public health and economic viewpoint to improve investigations regarding the mortality rates associated with pregnancy losses.

While the importance of research on maternal mortality is widely recognized, it has appeared increasingly evident to the authors that insufficient attention has been devoted to examining the subset of women's deaths following pregnancy losses. Greater insight into this subset of deaths may help to guide and prioritize the development of proactive health initiatives that can save women's lives and improve health.

Therefore, the authors identified the need for a systematic review which would provide (a) a description and synthesis of all the available qualifying literature, including proposals for research priorities and actionable interventions based on the best available evidence, and (b) a quantitative meta-analysis of the available evidence. To meet these goals, we determined that we should first seek to identify all record linkage studies examining mortality rates associated with pregnancy outcome regardless, without any limitation on time frame. This initial assessment would help us to identify any missed opportunities for examining pregnancy loss associated mortality. Second, we seek to identify all record linkage studies that have specifically examined death rates associated with pregnancy losses, including voluntary and therapeutic terminations. Using this subset of studies, we would then (a) develop a narrative synthesis of the common and specific findings of the relevant studies and (b) undertake a meta-analysis of any comparative mortality rates associated with different pregnancy outcomes which are appropriate to the methods of meta-analyses.

The importance of this investigation is underscored by numerous studies which have found that that parity and the exposure to various pregnancy outcomes has significant effects on life expectancy.[23–25] Record linkage studies examining pregnancy associated life expectancy are needed to help to identify how the number of pregnancies, number of deliveries, and types of pregnancy outcomes may affect the health and longevity of women. These findings, in turn, may then contribute to better screening to identify the subsets of women who may most benefit from interventions to ameliorate any harmful effects and/or to enhance any beneficial effects associated with pregnancy and pregnancy management.

## Definitions

*Pregnancy loss*, as used herein, includes all pregnancy outcomes that do not end in a live birth.[2]

*Natural loss* is a subset that includes all pregnancy losses except TOP. While the vast majority of natural losses are miscarriages, it should be noted that some researchers have chosen to report only on miscarriages while others have included ectopic pregnancies, still births and other natural losses together. Still other investigators have grouped women who had stillbirths with women who had live births since these pregnancies continued to term or near term.[1]

*Pregnancy associated death*, has been defined by the American College of Obstetricians and Gynecologists (ACOG) and the United States' Centers for Disease Control (CDC) to include all deaths during pregnancy or within one year of a pregnancy outcome regardless of presumed cause of death.[26] The identification of pregnancy associated deaths has been recognized is an important precursor to efforts to identify maternal deaths, which are defined to include only those deaths for which there is a medical opinion that some aspect of the pregnancy or pregnancy management was a contributing cause of death.[26]

*Pregnancy associated long-term mortality* is defined to include all deaths following one or more pregnancy outcomes without an imposed time limit. While the time limits used in each study reporting pregnancy associated long-term mortality should always be noted, this definition avoids establishing any arbitrary time limits and prepares the way toward calculating pregnancy associated mortality and life expectancy rates relative to variables such as gravidity, parity, live births, and exposure to pregnancy losses.

*Abortion related deaths* are defined by the CDC as any "death from a direct complication of an [induced] abortion (legal or illegal), an indirect complication caused by a chain of events initiated by an abortion, or an aggravation of a pre-existing condition by the physiologic or psychologic effects

of abortion."[27] The deliberate choice to place no time limit on the definition of TOP related deaths reflects the fact that there is no clear temporal limit on physiological and psychological effects that may contribute to subsequent death.

*TOP associated deaths (or abortion associated deaths)* are herein defined as the subset of pregnancy associated deaths which are within one year of a TOP. The one year limit corresponds to that for "pregnancy associated deaths."

TOP *associated long-term mortality* is an extension of the CDC's "abortion related deaths" and include all deaths among women with a history of TOP without regard to time. Just as the systematic identification of early and late maternal deaths must be preceded by a systematic identification of pregnancy history, so the identification of *abortion related deaths* should be preceded by the systematic identification of TOP history without a predefined time limit.

## Materials and methods

PRISMA guidelines were consulted and employed where appropriate in the development and writing of this review.

### *Eligibility criteria*

The first level of predefined eligibility criteria were: (1) the study was available in English; (2) the study examined mortality rates of women relative to one or more pregnancy outcomes; and (3) the study included systematic linking of death certificates to independent records used to identify if the deceased had one or more pregnancy outcomes within a year of her death. The independent records might be one of the following: birth certificates, fetal death certificates, TOP registries, paid insurance claims, or comprehensive hospital or medical records documenting treatments related to pregnancy.

The second level of eligibility criteria was to identify all publications meeting the first level of inclusion criteria which reported on death rates associated with any form of pregnancy loss (miscarriage, legal TOP, ectopic pregnancy, still birth, or any other failed pregnancy) as identified through records independent of the death certificates. This step eliminated studies that examined only mortality rates associated with childbirth, or which failed to distinguish between deaths associated with childbirth and pregnancy loss. This step helped to both identify missed research opportunities and to identify the eligible studies which do have information regarding mortality rates associated with pregnancy loss but failed to report this data.

The third step was to identify studies eligible for inclusion in a meta-analysis. This subset was drawn from the list of studies meeting the second level of eligibility. This third level of eligible studies included only those that (a) report mortality rates within one year for all three pregnancy outcomes of interest (childbirth, natural losses, and TOP) and (b) provided the most recently relevant data, thereby excluding duplication of results when the same population of women were examined in more than one study.

### *Information sources and search terms*

In July of 2015, a SCOPUS search was conducted using the search ( ( ( TITLE-ABS-KEY ( maternal mortality ) OR TITLE-ABS-KEY ( maternal death ) ) ) AND ( ( TITLE-ABS-KEY ( record linkage ) OR TITLE-ABS-KEY ( linked records ) ) ) ) OR ( ( ( TITLE-ABS-KEY ( pregnancy associated mortality ) OR TITLE-ABS-KEY ( pregnancy associated death ) ) ) AND ( ( TITLE-ABS-KEY ( record linkage ) OR TITLE-ABS-KEY ( linked records ) ) ) ). A total of 458 records of potential interest was returned.

A MEDLINE search was conducted using the search ((("pregnancy associated mortality" OR "pregnancy associated death") AND ("record linkage" OR "linked records")) OR (("record linkage" OR "linked records") AND ("maternal mortality" OR "maternal death")). This search returned 20 references.

Additional candidates were identified using the "snowball method," the review of all references cited by eligible papers plus citations from other maternal mortality reviews.

*Study selection.* After elimination of duplicates, all titles and abstracts were examined to identify publications with a prospect for meeting the predefined inclusion criteria. Those deemed candidates for inclusion were retrieved for full text review and studied to determine which articles met the predetermined inclusion criteria. Assessments of those studies qualifying for both levels of inclusion criteria were conducted by two reviewers, with disagreements resolved by discussion.

*Risk of bias.* Studies qualifying for both levels of inclusion were scored for bias using the Newcastle-Ottawa Quality Assessment Scale (NOQAS) for cohort studies.

*Data collection for descriptive summary of literature.* Each study meeting the second level of eligibility was entered into a table identifying the source, population size, time period examined, types of pregnancy outcomes examined, means of identifying deaths and pregnancy outcomes, any confounding variables that were examined in the study, NOQAS score, and a summary of major findings. The table was completed by two reviewers, with disagreements resolved by discussion.

*Data collection for meta analysis.* To calculate the age adjusted number of deaths in the first year for each subgroup's population for our meta-analysis we extracted data relative to the reported age adjusted risk of death during the first year following the pregnancy outcome from each country. To avoid duplication of cases, only the most recent study for each country

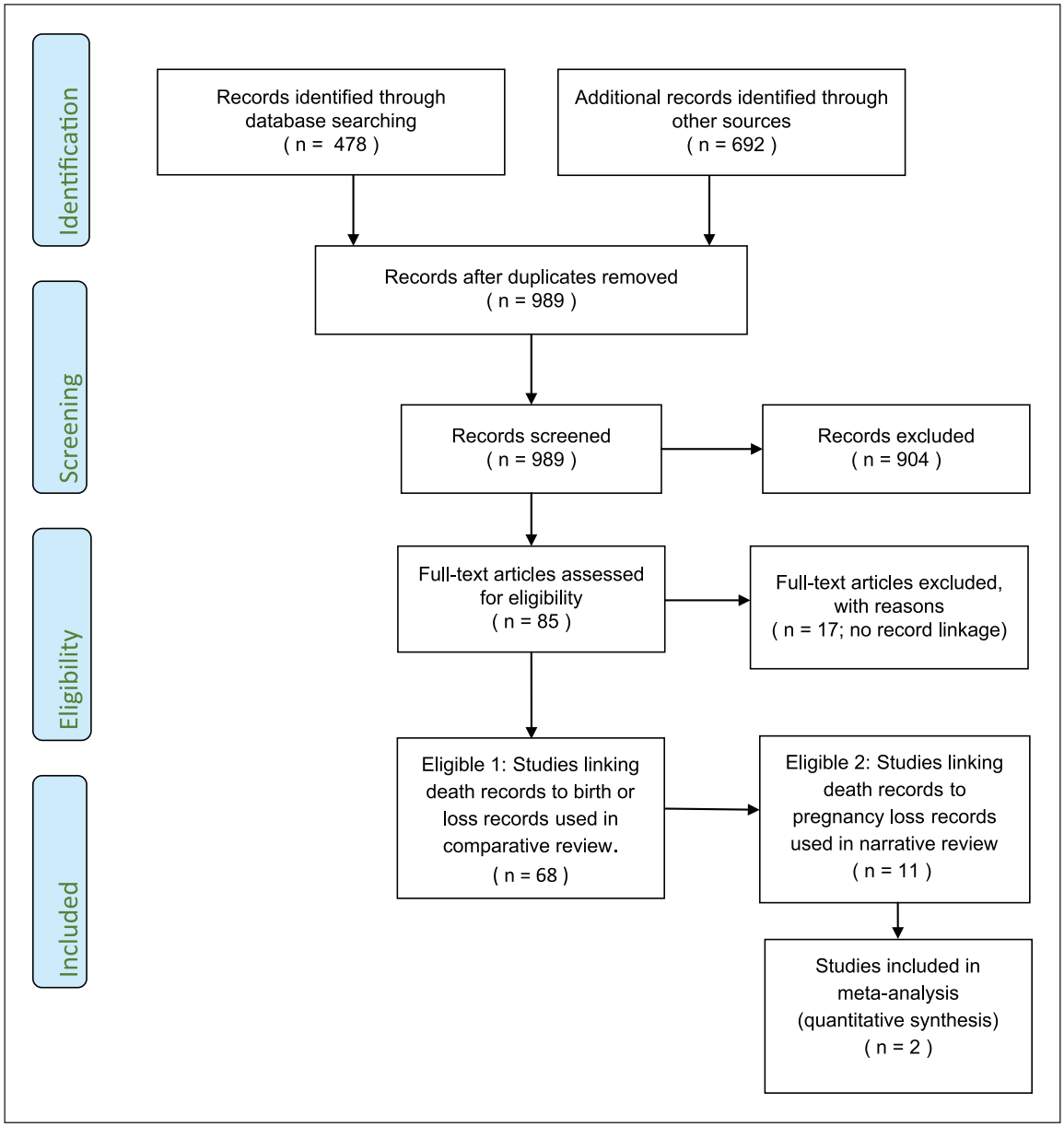



**Figure 1.** Flow chart of search results, reasons for exclusion, and three levels of inclusion.

was used in the meta-analysis. Using the age adjusted mortality rate of delivering women as the control in each case, odds ratios and confidence limits for each subgroup (TOP vs birth, and natural losses vs birth) and for each study were calculated using EpiInfo 7's StatCalc. These results were then entered into the Comprehensive Meta Analysis software package to produce results using the fixed effects model.

## Results

After removal of duplicates, a total of 989 titles were identified by the combination of search terms and review of additional references (Figure 1). Review of abstracts eliminated 904 references. At the second level of review, 14 more were eliminated after full text review because they did not identify pregnancy history using record linkage. Three non-English studies were also identified, but their abstracts indicated that none included data on pregnancy loss associated mortality so English translations were not sought. Thus, a total of 17 studies were eliminated at this stage.

A total of 68 studies examining populations in 11 countries met the criteria for the first level of eligibility. All of the studies identified significantly more maternal deaths than would have been identified by reliance on death certificates alone.

Of the 68 studies identified, 57 included record linkage of only birth and death records. In other words, they lacked any data on deaths associated with pregnancy losses. The distribution by country of these studies was as follows: one in

Bangladesh,[28] one in Brazil,[29] two in Canada,[30,31] one in Denmark,[32] one in Italy,[33] three in Netherlands,[34–36] four in Sweden,[37–39] one in Taiwan,[40] six in the United Kingdom,[41–46] thirty-four in the United States including Puerto Rico,[47–79] and three reporting data from multiple countries for which at least one country's data used record linkage which met our criteria for inclusion.[80–82]

The remaining 11 studies met the criteria for the second level of eligibility: reporting results of linkage of death certificates to independent records of pregnancy loss. These included seven studies from Finland,[1,83–88] two from Denmark,[89,90] and two from the United States.[91,92] Two of these investigated only deaths in the year following TOP.[88,91] The remainder investigated pregnancy associated deaths and/or pregnancy associated long-term mortality relative to both birth and pregnancy loss.

Details of the eleven studies are summarized in Table 1. The column labelled "Confounding Variables Examined" identifies factors which were either (a) controlled for statistically, such as was commonly done in regard to age of the woman, or (b) controlled for by study design, such as restriction of the population to only the lowest economic class, or exclusion of women with prior psychiatric history, or (c) controlled for by showing segregated results for discrete groups, such as married and unmarried. The NOQAS assessment revealed that quality of these studies was very high, with low risk of bias. With a possible range from 0-9, (high corresponding to the highest quality) only the one very earliest study scored below 8.

Figure 2 shows the mortality rate per 100,000 person years for each outcome reported by the latest studies from each of Finland, Denmark, and the United States, showing cumulative mortality rates for both one year and two years. The graph illustrates that mortality rates remain elevated after pregnancy loss beyond one year. Notably, the mortality rate over two years, comparing results from Denmark and California, suggest that low income women are at higher risk but that socioeconomic effects do not fully explain the results. Alternatively, the difference may be due to only first pregnancies being examined in the Denmark study.

Figure 3 shows that the risk of death after pregnancy loss is most elevated in regard to deaths from external causes: suicide, homicide, and accidents compared to both delivering women and women who have not recently been pregnant.[87,92] The implication that psychological effects associated with pregnancy loss may contribute to deaths resulting from self-destructive or risk taking behavior is further supported by a finding of higher rates of death attributed to mental illness (RR = 3.21, 94% CI 1.11–9.27) following TOP, even after controlling for prior psychiatric history.[92]

As several the eleven studies undertook examined associations from a different perspective, a summary of their most important findings, including figures illustrating many of these findings, is provided below:

- Pregnancy loss associated mortality may be over twice that of birth associated mortality.[1] TOP associated mortality is higher than miscarriage associated mortality, which is higher than pregnancy and delivery associated mortality. (Figure 2)
- TOP associated mortality rates are higher than birth associated mortality during the first 180 days[89] and remains higher for six or more years.[89,90,92] (Figure 4)
- Differences in pregnancy associated life expectancy vary according to the type and number of exposures to various outcomes. Successful deliveries may mitigate some of the effects of pregnancy loss.[90,92] (Figure 5)
- There is a dose effect, whereby exposure to multiple pregnancy losses increases the negative effect on life expectancy whereas multiple births increases life expectancy.[90] (Figure 6)
- The risk of death associated with pregnancy loss remains elevated even after controlling for psychological differences and economic class.[92] (Figure 2)
- While the risk of death after pregnancy loss is most elevated in regard to deaths from violent causes,[87,92] there is also evidence that when risk of death after pregnancy loss is tracked beyond one year a significant higher risk is also associated with specific causes of natural death, such as circulatory disease (RR = 2.87, 95% CI 1.68–4.89)[92]

The meta-analysis used age adjusted mortality rates for each pregnancy outcome reported in most recent studies of the population of Finland[86] and Denmark.[89] While the eleven studies included data on women in three countries, neither American study reported age adjusted mortality rates for the first year after pregnancy outcome.

Figure 7 shows results of the meta-analysis using the fixed effects model. It illustrates the comparative risk of death in the first year after TOP compared to delivery and for the first year after natural losses compared to delivery. The risk of death during pregnancy and one year after a delivery the age adjusted pregnancy associated risk of death was 170 percent higher following a TOP (RR = 2.705; 2.243 < 95% CI < 3.263), and 84 percent higher following natural losses (RR = 1.843; 1.420 < 95% CI < 2.392). For all pregnancy losses compared to delivery, the risk was 137% higher (RR = 2.374; 2.038 < 95% < 2.764; Q-value = 8.220, P = .042). The $I^2$ statistic indicates that about 63% of the variation in the overall results is due to heterogeneity rather than chance.

## Discussion

Our systematic review found 68 studies employing record linkage of death certificates to independent records of pregnancy and pregnancy outcomes. In nearly every case, the authors reported that record linkage significantly improved the identification of maternal deaths and pregnancy associated deaths compared to reliance on death certificates alone. We concur with the opinion that the direct and indirect effects of pregnancy on women's mortality rates cannot be accurately accessed without record linkage between death certificates and other medical records.[1]

**Table 1.** Record linkage studies examining deaths associated with one or more types of pregnancy loss with notes regarding key findings.

| Study (year) Country | Population & Time Period (Births / TOP / Natural Losses / Deaths) | Records Examined and Linked | Confounding Variables Examined | Quality Score* Range 0–9 | Summary of Major Findings |
|---|---|---|---|---|---|
| Shelton and Schoenbucher[91] (1978) United States | All fertile-aged Georgia women in 1975–Feb 1976 (NA / 19,877 / NA / 1,610) | death certificates TOP certificates | none | 6 | In this exploratory study Georgia death certificates were used to identify ten deaths preceded by an abortion, With an average observation period of 8 months, the one year abortion associated mortality rate was 75.5 per 100,000 cases. Deaths included 2 suicides (one four days after the TOP), 3 homicides (all within 4 months), 3 attributed to accidents, one sudden death from "coronary occlusion," and one death from ovarian cancer (the woman was receiving chemotherapy at time of TOP). Record linkage was incomplete due to limited information on the TOP certificates. |
| Gissler et al.[83] (1996) Finland | All fertile-aged women, 1987–1994. (513,472 / 93,807 / 71,701 / 9,192) | death certificates birth certificates TOP registry hospital discharge | age social class marital status | 9 | National suicide study. 1,347 suicides identified. No suicides while pregnant were found. Compared to women not pregnant in the year prior to suicide, women who aborted were three times more likely to commit suicide (3.08, 95%CI 1.57 to 6.03), pregnant and delivering women were half as likely (0.52; 95%CI 0.19 to 1.41), and women who miscarried were not significantly different. Suicide risk was highest in first two months following the pregnancy outcome. |
| Gissler et al.[84] (1997) Finland | All fertile-aged women, 1987–1994. (513,472 / 93,807 / 71,701 / 9,192) | death certificates birth certificates TOP registry hospital discharge | age | 8 | All death certificates were linked to medical and TOP registry to identify pregnancy within a year prior to death. Only 22% of pregnancies were identified on death certificates. Record linkage to TOP and hospital discharge records doubled number of deaths identified compared to linkage to birth certificates alone. Compared to women not pregnant, the age adjusted mortality ratio was half for delivering women (0.50, 95%CI 0.32 to 0.78) and significantly higher following TOP (1.76, 95%CI 1.27 to 2.42). |
| Gissler and Hemminki[85] (1999) Finland | All fertile-aged women, 1987–1994. (513,472 / 93,807 / 71,701 / 9,192) | death certificates birth certificates TOP registry hospital discharge | age | 8 | Compared to women who were not pregnant in the year before death, women who had TOPs had an 81% higher rate of death (1.81, 95%CI 1.31 to 2.50), women who gave birth had a 53% lower risk of death (0.47, 95%CI 0.30 to 0.74), and those who miscarried were not significantly different (0.85, 95%CI 0.58 to 1.24). 34% of deaths were from external causes. Women who had TOPs had significantly elevated risk of death from suicide, accidents, and homicides. Risk of death from natural causes was significantly lower for women giving birth (0.47, 95%CI 0.25 to 0.86) and for women who miscarried (0.39, 95%CI 0.20 to 0.75). |

**Table 1.** (Continued)

| Study (year) Country | Population & Time Period (Births / TOP / Natural Losses / Deaths) | Records Examined and Linked | Confounding Variables Examined | Quality Score* Range 0–9 | Summary of Major Findings |
|---|---|---|---|---|---|
| Reardon et al.[92] (2002) United States | Medicaid eligible and fertile aged women in California with pregnancy outcome in 1989 (116,936 / 56,343/ NA / 1,294) | death certificates all paid medical claims | age economic class 12–18 months prior psychiatric history | 9 | Medical records for women with a Medicaid treated pregnancy in 1989 were linked to death certificates. After controlling for psychiatric history and age, women who had a TOP were at significantly higher risk of death. The relative risk was 2.03 (95%CI 1.33 to 3.10) in the first two years following pregnancy outcome, 1.98 (95%CI 1.25 to 3.15) in years three and four, and declined to an insignificant 1.35 (95%CI 0.89 to 2.05) in the fifth and sixth years, and 1.29 (95%CI 0.84 to 1.96) in the seventh and eighth years. Multiple pregnancy outcomes significantly affected mortality rates. During the eight years following pregnancy, women who aborted had a significantly higher age-adjusted relative risk of death compared to delivering women from all causes (1.61, 95%CI 1.30 to 1.99), suicide (3.12, 95%CI 1.25 to 7.78), and homicide (1.93, 95%CI 1.11 to 3.33), as well as from natural causes (1.44, 95%CI 1.08 to 1.91), circulatory diseases (2.00, 95%CI 1.00 to 3.99), and cerebrovascular disease (4.42, 95%CI 1.06 to 18.48). |
| Gissler et al.[1] (2004) Finland | All fertile-aged women, 1987–2000. (865,988 / 156,789 / 118,490 / 15,823) | death certificates birth certificates TOP registry hospital discharge | age | 8 | All death certificates were examined. A total of 419 deaths were among women pregnant in the year prior to death. Without record linkage, 73% of pregnancy associated deaths would have been missed. Following live or still birth, 27% of deaths within 42 days and 78% of deaths from 43–364 days would have been missed without record linkage. Following TOP 71% of deaths within 42 days and 97% of deaths between 43–364 days would have been missed without record linkage. Following miscarriage or ectopic pregnancy, 54% of deaths within 42 days of pregnancy outcome and 94% of deaths between 43–364 days would have been missed. |
| Gissler[86] (2004) Finland | All fertile-aged women, 1987–2000. (865,988 / 156,789 / 118,490 / 15,823) | death certificates birth certificates TOP registry hospital discharge | age | 8 | One-year age adjusted mortality rates were calculated for women not pregnant in the year prior to death and compared to age adjusted mortality rates of three groups of women who were pregnant at death or during the year prior to death. The death per 100,000 was 57.0 for not recently pregnant women, 28.2 for delivering or pregnant women (RR 0.49, 95% CI 0.43–0.56), 51.9 for women who miscarried (RR 0.91, 95% CI 0.71 to 1.17), and 83.1 for women who had TOPs (RR 1.45, 95% CI 1.22 to 1.73). Women aged 25–34 who had TOPs were significantly more likely to die of circulatory system disease compared to not recently pregnant women, delivering women, and those who miscarried (rates per 100,000, respectively: 8.7; 4.4; 3.3; 1.5). |

*(Continued)*

**Table 1.** (Continued)

| Study (year) Country | Population & Time Period (Births / TOP / Natural Losses / Deaths) | Records Examined and Linked | Confounding Variables Examined | Quality Score* Range 0–9 | Summary of Major Findings |
|---|---|---|---|---|---|
| Gissler et al.[87] (2005) Finland | All fertile-aged women, 1987–2000. (865,988 / 156,789 / 118,490 / 15,823) | death certificates birth certificates TOP registry hospital discharge | age | 8 | This study examined only deaths from external causes. The death rate from external causes per 100,000 was 24.2 for women who had not been pregnant, 10.2 for those giving birth, 35.2 for those with natural losses, and 60.3 for those who had TOPs. The tables present segregated results show death rates from suicide, homicide, and those classified as accidental varied significantly by age and pregnancy outcome. The authors endorse recommendations for routine post-TOP checkup screening for depression and psychosis in the weeks following a TOP. |
| Reardon and Coleman[89] (2012) Denmark | All fertile-aged whose first pregnancy was in 1980–2004. (318,646 / 119,179 / 25,648 / 2,238) | death certificates birth certificates TOP registry hospital discharge | first pregnancy age at time of pregnancy; year of woman's birth | 9 | Age and maternal birth year adjusted mortality rates following first pregnancy outcomes were calculated over numerous time periods. Deaths rates for the first and second year are shown in Figure 1. Cumulative TOP associated mortality was significantly higher for every time period examined from 180 days to 10 years for both early and later TOP. The cumulative odds ratio for early TOP declined from a high at 180 days (2.03, 95% CI 1.11 to 3.71) to a low at ten years (1.39, 95% CI 1.22 to 1.60). Mortality rates associated with miscarriages were lower than for TOP and were significantly higher than for birth for periods over four years. |
| Coleman et al.[90] (2013) Denmark | All fertile-aged women, 1980–2004. (438,134 / 171,582 / 111,205 / 5,137) | death certificates birth certificates TOP registry hospital discharge | year of woman's birth age at last pregnancy number of births number of TOPs number natural losses | 9 | This study examined all causes of death using 25 years of data using numerous control variables, including exposure rate to various pregnancy outcomes. A dose effect was observed as shown in Figure 6. Exposure to various combinations of pregnancy outcomes was significant. The rate per 100,000 was 352 experiencing only births, 365 for those with both birth and natural losses, 541 for those with both births and TOP, 549 for those with no pregnancies, 550 for those with births, TOP and natural losses, 805 for those with only natural losses, and 1281 for those with only TOP. These findings suggest that TOP combined with natural loss compounds the risk of reduced longevity while a successful birth may reduce the risks associated with pregnancy loss. |
| Gissler et al.[88] (2014) Finland | All fertile-aged women, 1987–2012. (NA / 284,751 / NA / 3,798) | death certificates TOP registry | age | 8 | Based on prior research associating TOP with higher suicide rates, unofficial guidelines in Sweden recommended 2–3 week post-TOP assessments of psychological adjustment. These guidelines were made official in 2001. This study sought to examine if the guidelines adopted in 1996 may have reduced TOP associated suicide rates. The elevated risk of suicide after TOP declined from 2.84 (95% CI, 2.05 to 2.93) before 1997 to 2.44 (1.80 to 3.32) for 1997 thru 2012, but the drop was not statistically significant. |

*Details of the Quality Score assessment can be viewed at: https://docs.google.com/spreadsheets/d/1T0GySPufF4MXnuTNwmiDgcqHf1yh66UIso1AotTP8IQ/edit?usp=sharing

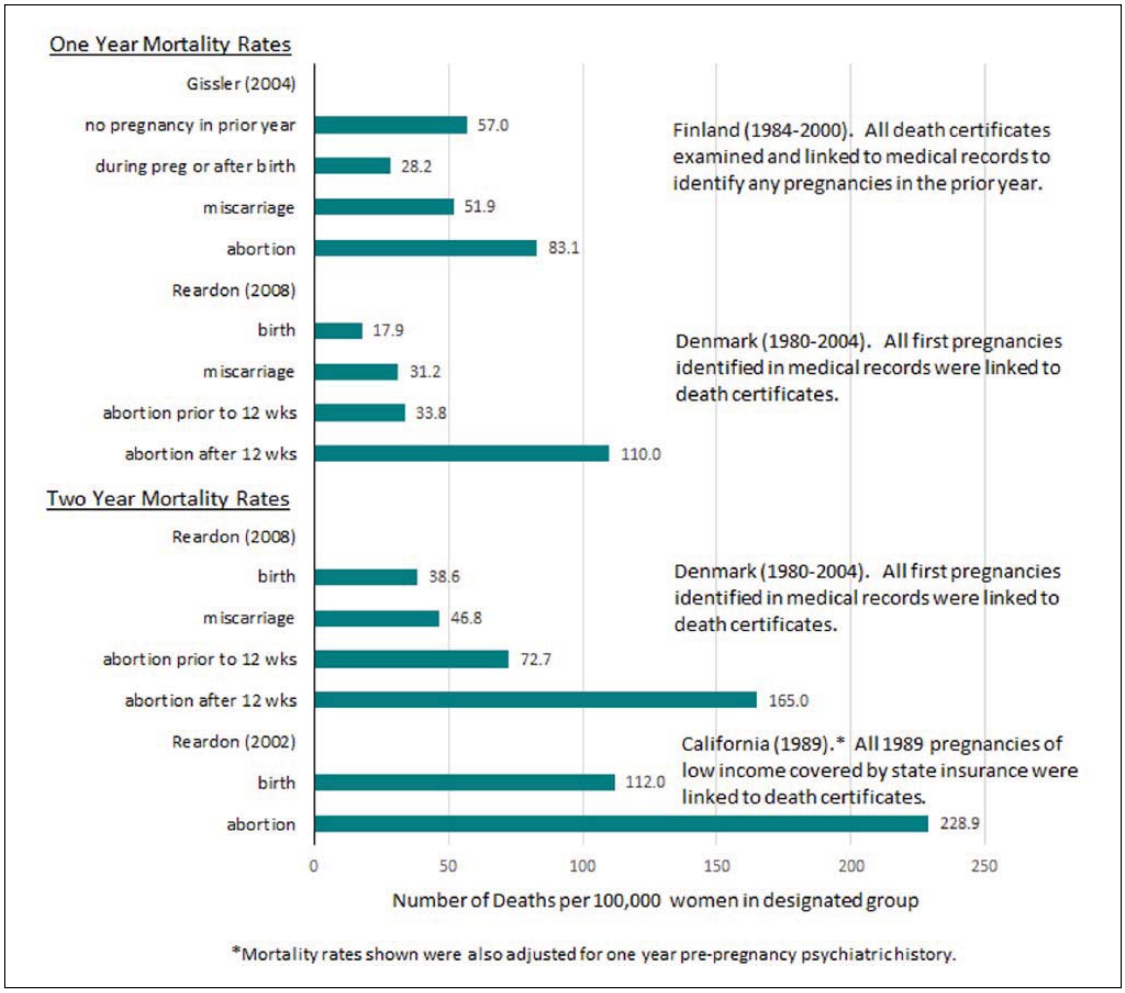



**Figure 2.** Cumulative Age Adjusted, All Cause Mortality Rates per 100,000 Women for One and Two Year Periods Following Pregnancy Outcome.

This systematic review also revealed that every record linkage study examining mortality rates relative to different pregnancy outcomes has revealed that pregnancy loss is associated with a higher risk of death than childbirth. These studies also show that this elevated mortality risk persists over many years, is multiplied by repeat exposure to pregnancy loss, and may be reduced by successful deliveries. The quality of these eleven studies is very high, with all but the one earliest attempt scoring 8 or above on the NCQAS (with a range 0–9).

Overall, the meta-analysis revealed that pregnancy loss associated mortality is more than double that of delivery associated mortality. Notably, the Danish data used in the meta-analysis included *only* first pregnancy outcomes while the Finnish data included all pregnancy outcomes. This may explain the higher pregnancy loss mortality rate observed in the Finnish data since a significant portion of the Finnish subjects would have been exposed to multiple pregnancy losses for which a dose effect of increased mortality risk has been observed.[90]

A disproportionate share of pregnancy loss associated deaths are due to suicides, accidents, or homicide.[83,86,87,92] In case study reports from mental health professionals and surveys of women struggling with pregnancy loss issues heightened risk taking and self-destructive behaviors are reported which may contribute to rates of accidents and homicide, in addition to suicide.[93] Risk of death from accidents and homicide may also be impacted by the elevated risk of substance abuse associated with TOP.[10–12] This hypothesis is supported by one U.K. study of pregnancy associated deaths that reported that[1] a major portion of accidental deaths were due to drug overdose, and[2] of eight women who died after being struck by cars as pedestrians, seven were drug users.[43] These findings underscore the importance of record linkage as a precursor to efforts to evaluate "abortion related deaths," as defined by the CDC.[27]

### *Strengths and weaknesses*

A strength of the narrative portion of this review is that while only 11 of 68 record linkage studies of mortality rates associated with pregnancy included examination of deaths associated with pregnancy losses, these eleven examined a

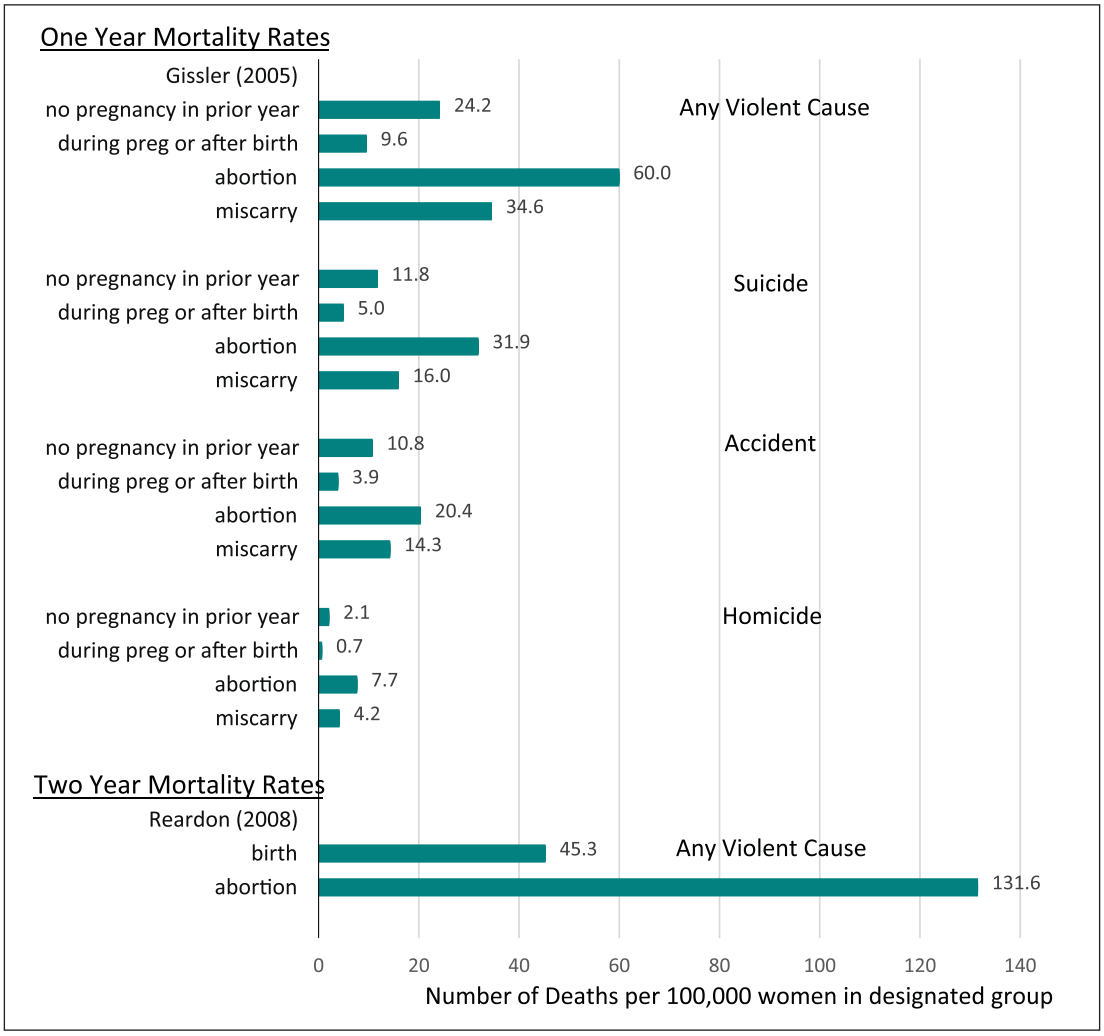



**Figure 3.** Cumulative Age Adjusted, Violent Cause Mortality Rates per 100,000 Women for One and Two Year Periods Following Pregnancy Outcome.
*Mortality rates shown were also adjusted for one year pre-pregnancy psychiatric history.

variety of different time frames and confounding variables, including economic class, marital status, age, number and types of prior pregnancy outcomes, and prior psychiatric history. At the same time, however, it is also a weakness that all of these confounding variable were not addressed in every study. The fact that all of these studies, despite variations, showed a consistent trend in findings indicates that the trend is a real one and is likely to replicated if applied to other populations.

Clearly, a priority of future research should examine a broader number of confounding variables across more populations to better understand the direct and indirect pathways and co-occurring risk factors that may guide future interventions. Future studies should seek to control for potential confounders including: income inequality, psychiatric history, access to medical care including birth control, intimate partner violence, intentionality of pregnancy, and level of maternal attachment to the pregnancy.

A major weakness of our meta-analysis is that data on mortality rates in the first year following pregnancy losses were only available from two countries, which highlights the failure of most researchers to address this issue. In addition, a minor weakness is that the Danish study included stillbirths in the natural loss grouping while in the Finnish study stillbirths were included in delivery category. Since the number of stillbirths were not reported, we could not adjust for this difference. But given the expected low number of stillbirths, this difference in categorization is very unlikely to have a major impact on the results. Another inconsistency is that all the studies from Finland included deaths during pregnancy in with deaths following a delivery (live or stillbirth), potentially adding nine months mortality risk to the one-year post-delivery mortality rate. This would tend to inflate deaths associated with delivery. Reporting deaths during pregnancy as a separate item would be preferable. These points highlight why more consistent classification standards would be helpful in future research.

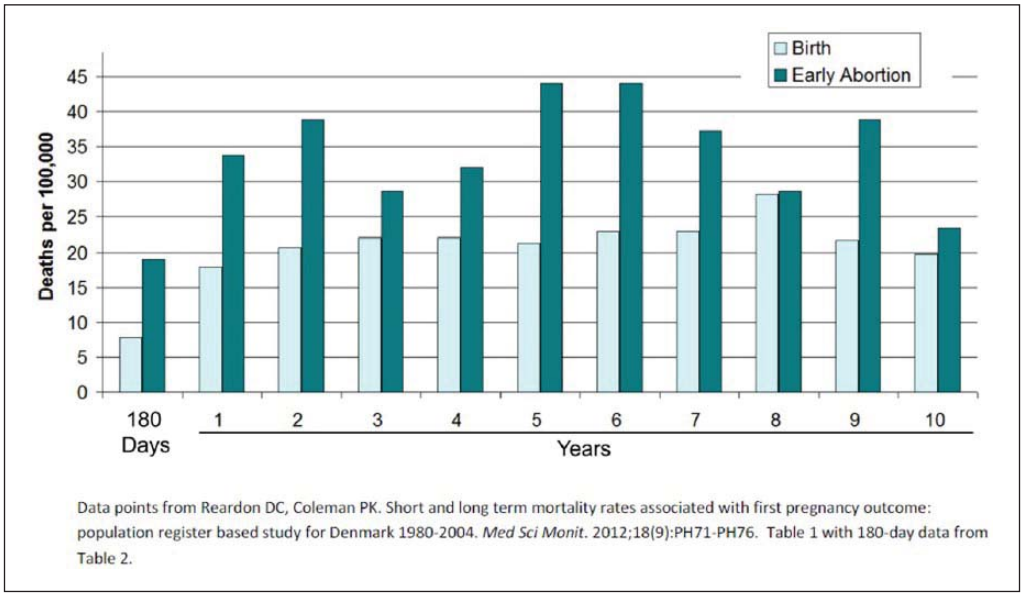



**Figure 4.** Death rates following first pregnancy outcome through 180 days and during each of the first through tenth years after pregnancy outcome.

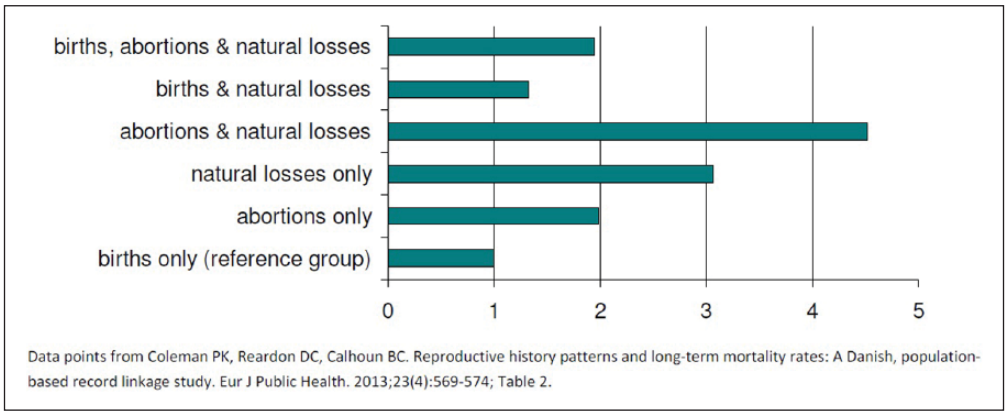



**Figure 5.** Adjusted odds ratios for pregnancy associated long-term mortality by exposure to types of pregnancy outcomes. Adjusting for age at last pregnancy and number of pregnancies.

In our opinion, any pregnancy that fails to produce a live birth should be treated as a pregnancy loss since there may be grief issues impacting future health. Rare cases of multiple gestations including both live birth and fetal loss are confounding and should be excluded from more general analyses or treated as a separate group.

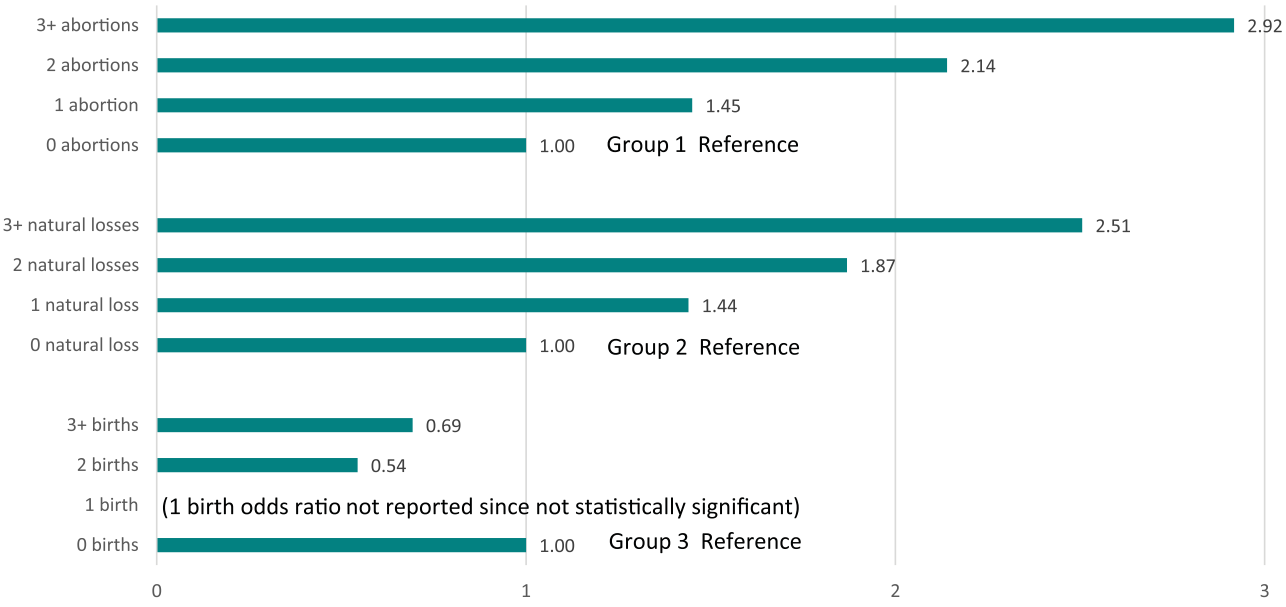
## *Future research and missed opportunities*

Unfortunately, many opportunities to investigate pregnancy associated mortality and long-term mortality have been missed, to date. Our literature review found that only 11 of 68 record linkage studies (and only 2 of 37 studies in the United States) explored mortality rates associated with pregnancy loss.

This oversight can and should be corrected. Even in countries without central TOP registries, such as exist in Finland and Denmark, exposure to TOP and miscarriage can be identified through medical records and insurance claims, as shown by researchers in the United Kingdom,[15] Canada,[22] and in the United States.[91,92] Unfortunately, except for these rare exceptions, most of the leading investigations into pregnancy associated deaths in Canada, the United Kingdom and the USA have failed to use these same techniques to investigate deaths associated with TOP or miscarriage.

Another missed opportunity appears to have occurred in a study of Italian women[33] in which researchers report that they did, in fact, link death certificates to records of terminations and miscarriages, but unfortunately their published analyses failed to provide any breakdown of death rates relative to each pregnancy outcome. Our request for a breakdown of deaths associated with each type of pregnancy outcome was rejected.

The failure of so many studies to report on pregnancy loss associated deaths indicates that there may be a risk of reporting bias. For example, social, political, or academic




All data from Table 4 of Coleman PK et al, Reproductive history patterns and long-term mortality rates: A Danish, population-based record linkage study. *Eur J Public Health.* 2013;23(4):569-574.

**Figure 6.** Adjusted Odds Ratios for Pregnancy Associated Long Term Mortality Rates by Frequency of Exposure to Each Pregnancy Outcome—Denmark 1980–2004.
Group 1. The odds ratios for exposure to abortion are adjusted for age at last pregnancy, number of births and number of natural losses.
Group 2. The odds ratios for exposure to natural loss are adjusted for age at last pregnancy, number of births and number of abortions.
Group 3. The odds ratios for exposure to birth are adjusted for age at last pregnancy, number of natural losses and number of abortions.
All data from Table 4 of Coleman PK et al.[90]

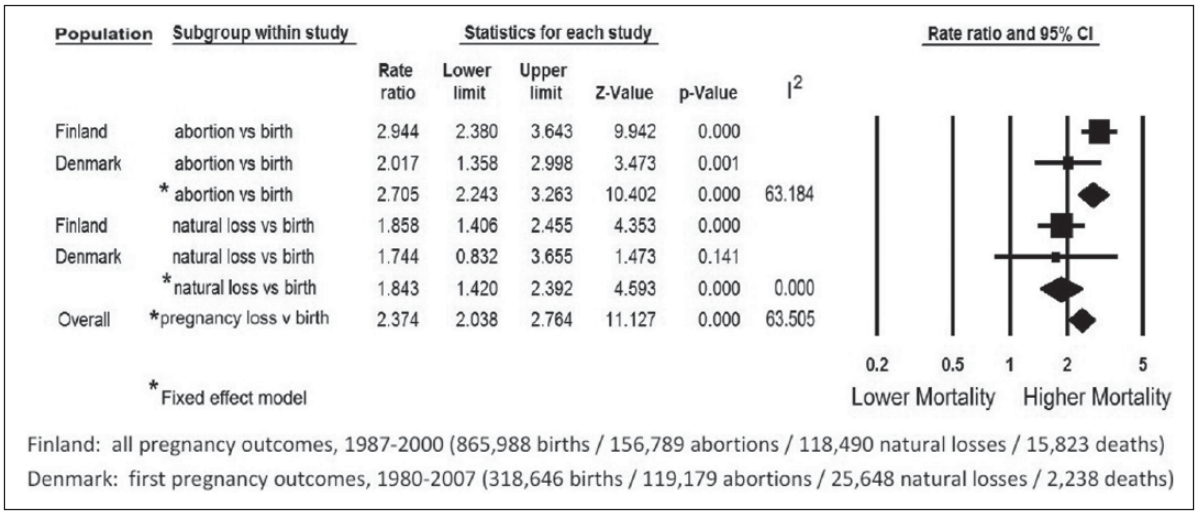



**Figure 7.** Meta-Analysis of Age Adjusted One Year Mortality Rates Associated with Comparative Pregnancy Outcomes.

sensitivities relative to efforts to promote legalization of safe abortion in developing countries may produce a bias against investigating and/or publishing findings that may show TOP is associated with an increase in mortality rates.[94,95] On the other hand, even though such findings have been reported since at least 1997,[83,84] there may also be lack of sufficient awareness among researchers regarding the elevated mortality rates associated with pregnancy loss. In either case, it is clear that in most countries where record linkage studies have been performed there *are no structural obstacles* to expanding record linkage studies to include pregnancy loss associated mortality. What is required is simply the academic and/or political will to undertake such investigations.

What is already sufficiently clear is that mortality rates and longevity are significantly affected by exposure to pregnancy losses, whether natural or induced. Therefore, in the interests of patients, future investigations into pregnancy associated mortality should *all* include efforts to identify and report on the comparative effects associated with prior exposure to TOP, miscarriage, and other natural losses. Such research is necessary to guide the development of better screening and treatment strategies for those subsets of women who may most benefit from targeted interventions.

### *Incidental or causal relationships?*

As discussed above, termination of pregnancy remains a sensitive and politically charged issue, for both those who defend it as a fundamental woman's right and those who oppose it for moral reasons. In our experience, these passions often inspire a hypercritical level of suspicion regarding any epidemiological findings which run counter to preconceived expectations.

For readers to access their own biases regarding this subject matter, simply imagine if our results were all reversed and the risk of death in the year following a TOP was half that associated with childbirth. Would the reader consider such reversed results more comfortable or more disturbing? Would such results provoke more confidence in the value of record linkage studies or more suspicion?

In either event, it is important to interpret these findings in as balanced a perspective as possible. Correlation does not prove causation. There may be common risk factors for pregnancy loss which explain the elevated risks.[96] Indeed, given the fact that a disproportionate number of deaths associated with prior pregnancy loss are due to suicide and accidents, it would appear that causal contribution would most likely be indirect and chiefly mediated by psychological effects which are known to occur among women who experience a pregnancy loss.[2–10,17–19] Moreover, the finding that there pregnancy loss has a dose effect on increased risk of death[90] (Figure 6) strongly parallels the finding of pregnancy loss having a dose effect on increased risk of mental illness.[2,5,13]

But even if the elevated risks can be entirely explained by common risk factors, it is critically important to acknowledge that these findings are still clinically relevant and very useful. Why?

Because a history of pregnancy loss is at least a *useful marker* for identifying women who may need additional screening, counselling and care. Therefore, alert clinicians can and should screen for a history of pregnancy loss in order to use this actionable information as detailed in our clinical recommendations below. How this marker may be used to provide better screening and referrals will be discussed more fully in the next section.

Additional support for a causal interpretation is found in studies which have identified the first onset of psychological problems, such as sleep disorders[17] or substance abuse,[97] soon after a pregnancy loss among women who did *not* previously have these problems.[13] Another important study examined hospital admission rates for attempted suicide rates prior to pregnancy and after a TOP[15] and revealed a significant and dramatic shift from a "normal" rate of suicide attempts to an elevated rate after TOP, as seen in Figure 8. These findings led the researchers to conclude that "the increased risk of suicide after an induced abortion may therefore be a consequence of the procedure itself."

Another factor to consider regarding the question of causality is that negative effects may be substantially limited to small subgroups of women who are at greater risk. For example, experts on "both sides" of the legal abortion controversy are actually in agreement regarding the evidence that women who feel coerced or pressured into unwanted TOP are at greater risk of serious complications, including elevated self-destructive tendencies.[98] If we were to hypothesize, then, that all of the elevated risk of death associated with TOP reported in the studies we examined are limited to cases of coerced TOP, it would then follow that the findings reported herein may be an indirect measure of the frequency of coerced TOP. Such a conclusion would only further underscore the importance of the clinical recommendations offered in the next section.

Perhaps the most powerful evidence that pregnancy loss contributes directly to mental health problems is the frequency with which self-aware, introspective women specifically attribute the onset or worsening of substance use, depression, flashbacks, sexual dysfunction, self-destructive tendencies and other issues to their pregnancy loss experiences.[93,99,100] These self-assessments are further validated by therapists treating women for pregnancy loss related issues.[101,102] Additionally, evidence that post-abortion counselling programs reduce symptoms of psychological illness[103] also support the hypothesis that TOP can trigger or exacerbate psychological illness; after all, an effective treatment is evidence for an accurate diagnosis.

We are not asserting that pregnancy loss is the *sole* cause of the elevated risk of death identified in these studies, but rather that there is ample evidence to believe pregnancy loss can be a *contributing* cause. The discussion above is therefore intended to emphasize the importance of research designed to better understand the causal pathways and co-occurring risk factors which can then be used to better identify women who may benefit from appropriate interventions.

### *Clinical recommendations*

Clinician's should be alert to the fact that a history of any pregnancy loss may impact many aspects of women's lives. Prior pregnancy losses, voluntary or involuntary, are also sensitive issues for many women which they may hesitate to dicuss. Therefore, it is highly recommended that as a standard intake question, or in periodic updating with patients, clinicians should make a gentle, non-judgmental query: "Have you had any pregnancy losses, like a miscarriage,

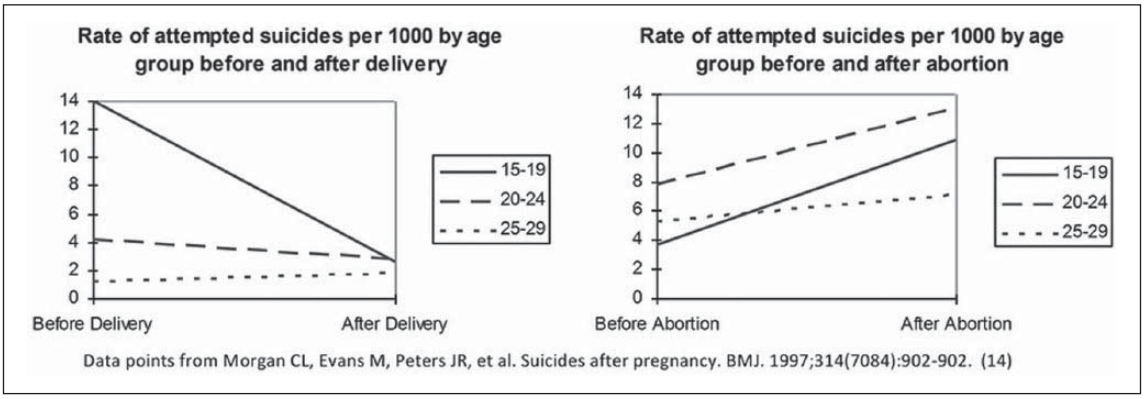



**Figure 8.** Rate of treatments for attempted suicide before and after delivery or TOP.

abortion, or still birth?" This query, which non-judgmentally names each type of pregnancy loss, gives women permission to discuss any sensitive feelings regarding past pregnancy losses and also opens up opportunities to discuss any lingering or intermittent concerns.

When women do report a prior pregnancy loss, or for women considering a termination of pregnancy, we recommend that clinicians should then investigate if additional risk factors are present. Especially useful in this regard, at least 15 risk factors for more severe reactions following TOP which have been identified by American Psychological Association Task Force on Mental Health and Abortion.[104] With slight modification, these risk factors can also be applied to miscarriage and other natural losses. They are:

- terminating a pregnancy that is wanted or meaningful
- perceived pressure from others to terminate a pregnancy
- perceived opposition to the abortion from partners, family, and/or friends
- lack of perceived social support from others
- various personality traits (e.g., low self-esteem, a pessimistic outlook, low-perceived control over life)
- a history of mental health problems prior to the pregnancy
- feelings of stigma; perceived need for secrecy
- exposure to antiabortion picketing
- use of avoidance and denial coping strategies
- feelings of commitment to the pregnancy
- ambivalence about the abortion decision
- low perceived ability to cope with the abortion
- history of prior abortion
- late term abortion.

These risk factors can and should be used to identify women who may need more counselling and other services. Given the dose effects observed, screening for a history of pregnancy loss is especially important in preparing treatment plans for women in all subsequent pregnancies. Therefore, we recommend the APA identified screening criteria should be used on at least four occasions: (a) when women seeking mental health care report any history of pregnancy loss, (b) when women are seeking care in anticipation of becoming pregnant, (c) upon diagnosis of a pregnancy, and (d) before termination of a pregnancy.

## *Summary*

Deaths associated with pregnancy, both within the first year and beyond, are significantly different relative to pregnancy outcome. Births have a positive effect on longevity while pregnancy losses have a negative effect, with negative effect of TOP being greater than that of natural losses. Multiple pregnancy losses are especially problematic. Pregnancy loss is at least a marker for adverse maternal outcomes, but is most likely a contributing risk factor driven by psychological stresses related to pregnancy loss.[2–22]

Many opportunities to investigate pregnancy loss associated long-term mortality rates have been missed. Future investigations into maternal mortality and pregnancy associated mortality should include systematic record linkage to medical and insurance records to identify pregnancy losses so that these patterns and risk factors can be better understood.

Screening for a history of pregnancy loss (induced or natural) is highly recommended as a means of identifying women who may benefit from additional counselling and interventions. Screening for risk factors associated with more psychological maladjustments following TOP, as identified by the APA,[104] is also highly recommended.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: No grants or outside funding were used. David Reardon's efforts were funded as part of his regular duties as Director of Research with the Elliot Institute. John Thorp's efforts were not funded.

## Ethical approval

Ethical approval was not sought for the present study because it is a literature review and does involve any original research using human or animal subjects.

## Informed consent

Informed consent was not sought for the present study because it is a literature review and does not involve any original research using human subjects.

## Supplemental files submitted

- Prisma Checklist.
- Spreadsheet of Newcastle - Ottawa Quality Assessment Scale: Cohort Studies.

## Trial registration

This was not a randomized clinical trial therefore it was not registered as such.

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